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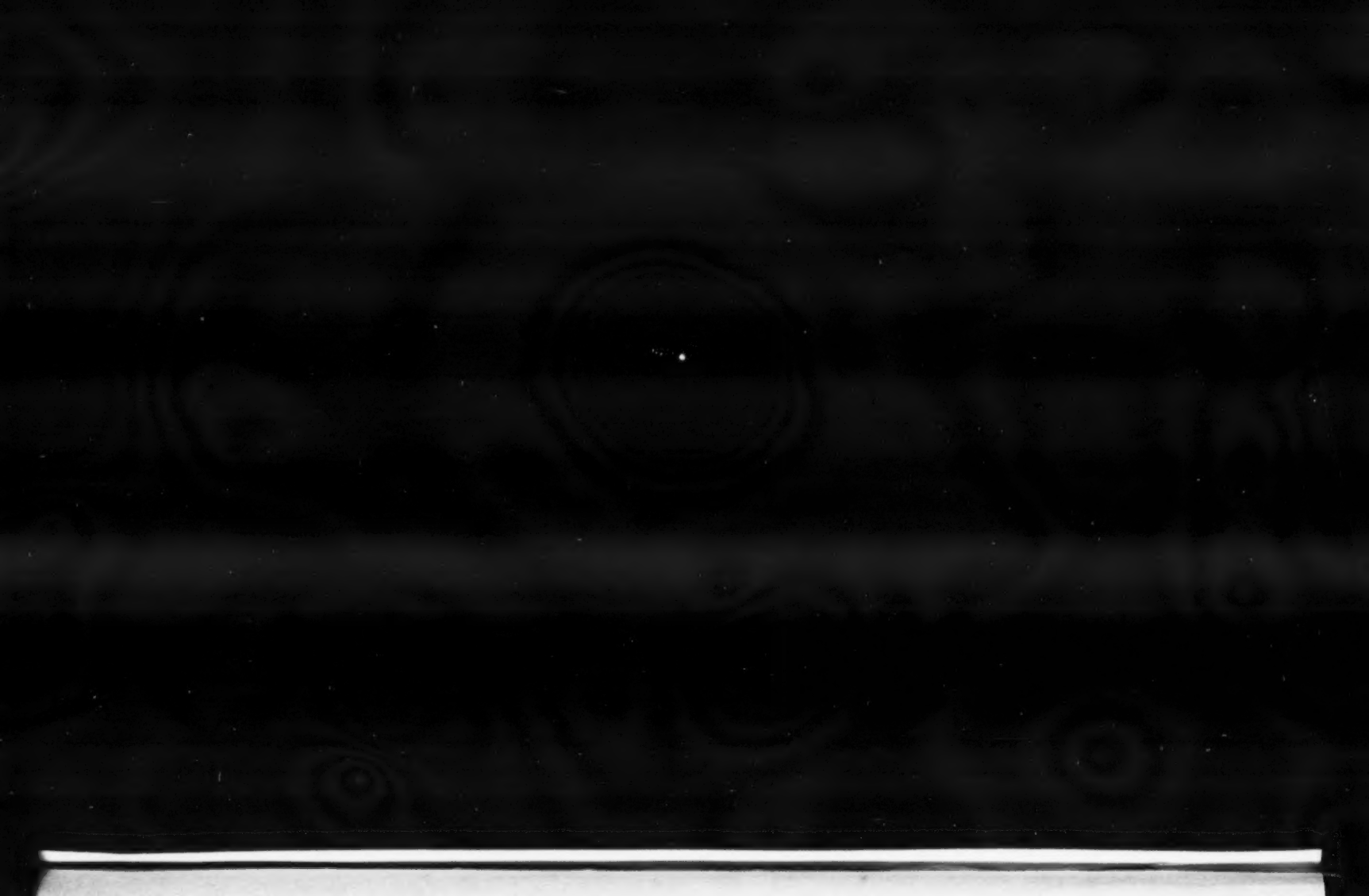

PARATHORMONE IN THE TREATMENT OF "RADIUM POISONING"[1]

A Preliminary Report

F. B. FLINN, Ph.D., and S. M. SEIDLIN, M.D.
New York

The "radium poisoning" cases referred to in this paper occurred among luminous dial painters and not persons exposed to gamma rays alone,—as for instance, individuals handling radium, its salts or solutions, or those exposed to x-rays. The intoxication in our cases resulted from the habit of pointing the brush between the lips. The luminous material consisted of a specially prepared crystallized zinc sulphide, very small amounts of radium, or a mixture of radium and mesothorium with minute additions of cadmium, copper and manganese to bring out the proper color. Because of the ingestion and absorption of small amounts of the material by the gastro-intestinal tract and subsequent deposition of the radio-active material in all the bones of the body,—probably as the phosphate and not the sulphate,—the organism is exposed to all three rays,—alpha, beta and gamma. There has been a studied attempt to place the entire blame for the condition on mesothorium, but it can be stated with absolute authority that only a portion of the girls who have suffered ill-effects from their industrial exposure used paint containing mesothorium,—the others used material containing radium alone as the source of radio-activity. The statement that mesothorium is alone to blame is absolutely without foundation.

As to the treatment of the "radium poisoning" all one can say is that no specific indications have been reported up to the present time. Treatment so far has been purely symptomatic, directed along the lines of hygiene of the mouth, prevention and treatment of sepsis, treatment of anaemias and general hygienic care.

J. C. Aub and his co-workers have recently reported in a series of

[1] Received for publication July 19, 1929.

articles the use of ammonium chloride, for the purpose of increasing the calcium elimination, and other similar experiments in the elimination of lead. He found that the ammonium chloride or phosphoric acid administration is very effective in the elimination of calcium and lead. The method is calculated to produce a temporary acidosis and convert the insoluble calcium and lead salts into soluble ones, and thereby raise the excretion of those metals.

The original work of MacCallum and Voegtlin, who found a lowering of the blood calcium in dogs after parathyroidectomy, was followed up by Collip's work who showed that the injection of his parathyroid extract[2] raised the blood calcium and increased the calcium excretion. Aub and his co-workers found that the latter is also true for man. Aub also found that calcium and lead metabolism run parallel in many respects. The administration of parathormone in patients with lead poisoning caused considerable excretion of calcium from the bones along with the excretion of lead. His experiments were carried out on patients while they were on a low calcium diet. The elimination of the above metals was slower when patients were on a high calcium diet.

The effect of parathormone on the calcium and lead excretion described by Aub has suggested our method of treatment of the radium victims.

In June, 1926, Flinn used ammonium chloride and parathormone in the treatment of a case. Because of objection from the patient to injections, the treatment was discontinued after four doses. The stools showed a definite increase in radio-activity during the treatment.

Since then we have treated three other cases, the treatment still being in progress. Two of these patients were placed in a hospital and parathormone injections given every other day, at first in very small doses of ten units which gradually were increased to forty. Frequent blood calcium determinations were made and always one preceding the injection of parathormone. Electroscopic tests were made of the stools. It is definitely established that there is a slight normal elimination of radio-active material by way of stools in these

[2] Parathormone—Eli Lilly & Co.

patients, but under treatment there was a definite increase in this elimination. At the end of a month the electroscopic tests of the patients themselves showed a decided decrease in the original readings prior to the instituting of the treatment. After a short rest these two patients were subjected to further treatment, the parathormone dosage being raised to fifty units every other day. Injections were given every other day rather than daily in order to avoid the cumulative effect with its dangers. Raising the blood calcium to a high level at intervals rather than keeping it at a continuous high level seemed more advisable, in view of Aub's findings. Aub says "The primary effect of parathormone is on phosphorus excretion rather than on calcium. Thus, when parathormone is administered, the first metabolic changes are a rise in phosphorus excretion and a fall in serum phosphorus; when parathormone is discontinued, the converse is true."

Electroscopic tests of the patients at the end of the second period showed still further diminution of their radio-activity. The general condition of both patients showed marked improvement. They both gained considerable weight, ten pounds in seven weeks, were feeling stronger and improved much in appearance. The third patient, a much more advanced case of radium poisioning, has been subjected to the same treatment. At the present time there are already indications of active elimination of radio-active substances under the parathormone treatment. The treatment of this patient is considerably complicated by a very marked destruction and infection of the lower jaw.

A short summary of these cases follows below, where only positive findings are given. All the bones of the patients were x-rayed by Dr. J. Steiner. The x-ray pictures in all these cases were very striking in that they showed lesions in the skull that seemed to be characteristic in this disease. These are sharply circumscribed round areas of rarefaction in the skull resembling those frequently seen in cases of myeloma or metastatic tumors. A piece of skull removed during autopsy of a recent case of "radium poisoning" showed similar x-ray lesions. These x-ray lesions and their pathology will be described in a later paper.

Case 1. History. The patient is a young girl of 24, who has worked continuously in a watch factory for a number of years. For about seven years she painted dials with luminous paint, pointing brushes in her mouth. Lately she has been working in other departments in the same factory where presumably she has not been exposed to radium. She had been in fairly good health up to a year ago when she began to complain of weakness, loss of weight and loss of energy. In February, 1929, her dentist thought he saw definite irregularities in both jaws. The patient is known to have been slightly radio-active since 1926.

Physical examination. Slight general undernutrition; negative otherise.

Period of treatment. April 12th, 1929 to June 8, 1929.

X-ray examinations. Showed round sharply circumscribed areas of rarefaction in the skull.

Therapy. The patient was kept on a normal diet with the addition of liver. Regulation of bowels; Blaud's pills II, t.i.d., p.c.; injections of Fraisse's ferruginous ampoules every other day.

Parathormone therapy. From April 12th to May 11th, parathormone was given intramuscularly every other day, beginning with ten units and gradually increasing to forty units.

From May 26th to June 8th, intramuscular injections of parathormone were given every other day—dosage forty to fifty units.

Blood calcium determinations were done at frequent intervals and one always preceding the parathormone injection. The level of the blood calcium varied in accordance with the time elapsed after the preceding injection of parathormone.

Results. 1. General. The patient's weight on admission was 99 lbs. Gained ten pounds during her stay in Hospital. General condition very much improved. She is feeling very much stronger and looks better.

2. Electroscopic measurements of stools. Showed increase in the elimination of radio-active material by the alpha-ray method, as treatment was given.

3. Electroscopic measurements of patient:

Before treatment:
Gamma ray:
Natural leak..... 0.00368 d/p/s
Patient..... 0.00302 d/p/s
Increase due to patient. 0.00066 d/p/s approximately = 7.8 micrograms
Expired air:
Natural leak..... 0.01041 d/p/s
Patient (3 hours)..... 0.01612 d/p/s
Increase..... 0.00571 d/p/s approximately = 1.2 micrograms
Total acticity (amount of radio-active material contained in patient).....approximately = 9 micrograms

After treatment:
Gamma ray:
Natural leak..... 0.00299 d/p/s
Patient..... 0.00336 d/p/s
Increase..... 0.00037 d/p/s approximately = 4.4 micrograms

Expired air:
Natural leak..... 0.08333 d/p/s
Patient..... 0.08569 d/p/s
Increase..... 0.00236 d/p/s approximately = 0.5 microgram
Total activity.....approximately = 4.9 micrograms
Deactivation = 45.6 per cent

Case 2. History. The patient is a young married woman of 25. Had worked in a clock factory seven years ago for a period of four months. Painted dials with luminous paint, pointing brushes in her mouth. Three years ago her dentist extracted some devitalized teeth. Four months ago two small sequestra came out from one of the cavities which failed to heal. X-ray plates disclosed considerable rarefaction of the jaw about the cavities where the teeth had been extracted and there was a failure of bone regeneration. She was then tested by one of us and was found to be radio-active. Five and a half months ago she gave birth to a healthy child, but had a stormy delivery followed by a post-partum streptococcus infection. For six weeks she had chills and fevers, and finally underwent a complete hysterectomy. Since then has been troubled with night sweats off and on, also with a slight vaginal discharge. Her appetite is poor; complains of gases, *p.r.*, and slight constipation; very nervous; has been married seven years; has had no miscarriages; husband living and well. History negative otherwise.

Physical examination. General undernutrition. Uterus and adnexa removed. There is a fairly large cavity in the left upper jaw which failed to heal after the extraction of the teeth.

Period of treatment. From April 14th to June 7, 1929.

X-ray examinations. Showed round sharply circumscribed areas of rarefaction in the skull.

Therapy. General therapy the same as in Case 1.

Parathormone treatment. Same as in Case 1.

Blood chemistry. It is of interest to note that at the time the dosage of parathormone was forty to fifty units every other day the N.P.N. rose to 54 milligrams per 100 cc. and Urea N to 34.2 milligrams per 100 cc. This is a confirmation of similar findings in Aub's experiments.

Results. 1. General. The patient's weight on admission was 102 lbs.; gained ten pounds during the treatment. General condition very much improved. She is feeling very much stronger and looks better.

2. Electroscopic measurements of stools. Showed increase in the elimination of radio-active material by the alpha-ray method, as treatment was given.

3. Electroscopic measurements of patient:

Before treatment:
Gamma ray:
Natural leak..... 0.00923 d/p/s
Patient..... 0.01082 d/p/s
Increase due to patient. 0.00159 d/p/s approximately = 18.4 micrograms

Expired air:
Natural leak..... 0.00757 d/p/s
Patient (3 hours).... 0.01190 d/p/s
Increase..... 0.00433 d/p/s approximately = 1 microgram
Total activity (amount of radio-active material contained in patient).....approximately = 19.4 micrograms

After treatment:
Gamma ray:
Natural leak..... 0.00307 d/p/s
Patient..... 0.00374 d/p/s
Increase..... 0.00066 d/p/s approximately = 7.7 micrograms
Expired air:
Natural leak..... 0.00877 d/p/s
Patient..... 0.01134 d/p/s
Increase..... 0.00257 d/p/s approximately = 0.5 microgram
Total activity.....approximately = 8.2 micrograms
Deactivation = 57.7 per cent

Case 3. History. The patient is a young girl of 20. About five years ago she worked for ten months in a clock factory, using luminous paints and pointing brushes in her mouth. She had always been in good health until last August, 1928, when she had a left lower molar extracted because of a cavity and some pain. The cavity failed to heal. Three months later her dentist pulled out two small pieces of bone from the wound. The wound failed to heal during the following winter. The patient was very much annoyed by a very bad taste in the mouth. About three months before admission she began to have pains in the left lower jaw, left ear and left side of the head. Gradually the left lower jaw began to swell. A month later she went to another dentist who x-rayed the jaw and found an abscess which he drained. Soon a few small "lumps" appeared under the left lower jaw. These were tender and three weeks prior to admission she was compelled to stay in bed. A local physician was called in who stated that the glands were enlarged and advised hot applications. Another physician later advised ice applications. The latter produced a diminution of the size of the glands as well as in the swelling of the left side of face. The patient was examined by one of us and was found to be radio-active. History otherwise negative.

Physical examination. Slight general undernutrition; marked pallor; inability to open mouth; swelling of the left side of the face, left lower jaw and submaxillary lymphnodes.

Period of treatment. The patient is still under treatment, having been admitted June 8, 1929.

X-ray examinations. Showed round sharply circumscribed areas of rarefaction in the skull. Extensive necrosis of left lower jaw.

Therapy. General therapy the same as in Cases 1 and 2. Swelling under the left lower jaw was incised and is now being drained. A culture showed *Streptococcus non-hemolyticus.* A vaccine was prepared which is now being administered.

Parathormone treatment. Same as in Cases 1 and 2.

Results. 1. General. At the present time the patient looks better than on admission; has gained several pounds in weight and feels a little stronger. There is no pain in the jaw or face and the swellings of face, jaw and submaxillary lymph-nodes have somewhat subsided.

2. Electroscopic measurements of patient:

Case No. 3

*(2) Electroscopic Measurements of Patient:**

Before Treatment:
Gamma Ray:
Natural leak..... .00403 d/p/s
Patient..... .00774 d/p/s
Increase due to patient. .00371 d/p/s approximately = 43.6 micrograms

After Treatment:
Gamma Ray:
Natural leak..... .00368 d/p/s
Patient..... .00555 d/p/s
Increase..... .00187 d/p/s approximately = 22.0 micrograms

Deactivation = 50.5%

SUMMARY

Three cases of "radium poisoning" in luminous dial painters have been subjected to treatment by injections of Collip's Parathyroid Extract (Parathormone,—Eli Lilly & Co.). The first case showed a loss of 45.6 per cent of radio-activity in seven weeks. The second case showed a loss of 57.7 per cent in seven weeks. The third case showed a loss of 50.5 per cent in seven weeks.

All the three patients show characteristic x-ray lesions in the skull,—round sharply circumscribed areas of rarefaction. A piece of skull removed during autopsy of a recent case of "radium poisoning" showed similar x-ray lesions.

*The electroscopic determinations of this patient's expired air could not be carried out with accuracy on account of the patient's inability to open her mouth. Therefore we were compelled to judge the progress of the treatment on the basis of the Gamma Ray determinations alone.

THE CIRCULATORY FAILURE OF DIPHTHERIA[1,2,3]

I. The Clinical Manifestations of Early and Late Failure

FRANCIS F. SCHWENTKER and WILLIAM W. NOEL

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The history of diphtheria adds a romantic chapter to the annals of medicine. Centuries before its recognition as a clinical entity, the ancient physicians described cases which must undoubtedly have been diphtheria. Not only were they familiar with the membranous character of the diphtheritic exudate, but they have described symptoms which may be identified with some degree of certainty with the characteristic circulatory failure and death in this disease.

Aretaeus the Cappadocian (1) in the second century A.D. describes the Egyptian or Syric ulcer in the first book of his treatise on the causes and symptoms of acute diseases:

> "Ulcers occur on the tonsils; some indeed of an ordinary nature, mild and innocuous; but others of an unusual kind, pestilential and fatal. Such as are clean, small, superficial, without inflammation and without pain are mild; but such as are broad, hollow, foul and covered with a white, livid or black concretion are pestilential. And if the disease spread outwardly to the mouth and reach the columella (uvula) and divide it asunder, and if it extend to the gums, tongue and alveoli, the teeth also become loosened and black; and the inflammation seizes the neck; and these die in a few days."

The manner of death is described as most piteous, for the breath had a putrefactive odor so that the patients could not endure the smell of themselves. The countenance was pale or livid, the fever acute with

[1] Received for publication June 14, 1929.

[2] We are greatly indebted to Professor John J. Abel and Dr. E. M. K. Geiling for their interest in this work and for the laboratory facilities and to Dr. Myron G. Tull for the clinical material so kindly placed at our disposal.

[3] This paper and the two following received the William H. Howell Award of the School of Medicine, Johns Hopkins University, June, 1929. Ed.

a burning thirst and yet the patients dared not drink for fear of pain. Food was observed to regurgitate through the nostrils and the symptoms passing on from bad to worse, the patients suddenly fell to the ground and expired.

Further additions to the knowledge of this disease are to be found in the so-called Tetrabiblos of Aetius of Amida (2) who flourished in the sixth century of this era. "I have known a girl die even after 40 days when already on the way to recovery. But in most cases the danger lasts only seven days." Such descriptions are highly suggestive of the sudden deaths so dreaded in diphtheria.

During the dark ages which followed the decline of learning, reports were scanty and incomplete and the works of the European physicians through the 16th, 17th and 18th century epidemics added little to the existing knowledge. Strangely enough, Bretonneau (3), who established the first definite clinical criteria for the disease in 1821, seems not to have recognized the cardiac involvement, although his pupil Trousseau (4) observed cases of sudden collapse which could not be attributed to laryngeal stenosis and suffocation. Werner (5) in 1842 appears to have been the first observer to connect pathological conditions in the heart with the sudden death of diphtheria. Following this, more and more clinical observations finally led to the formulation of various theories for the cause of the collapse. These theories have been revised, added to, discredited and revived, until today we are richer by the works of hundreds of observers, but have yet to prove the truth or falsity of many of the theories.

It is interesting to follow the development of these hypotheses through to the present time. Any review of the great mass of literature, however, is not within the scope of this paper. Moreover, it would be useless to attempt to enlarge on the historical summaries of Warthin (6) and Marvin (7) to whose papers anyone interested may refer. Briefly, then, seven theories for the cardiac pathology in diphtheria have been advanced, which may be enumerated in chronological order as follows: 1. Cardiac thrombosis with paralysis (1842–1882). 2. Bacterial endocarditis (1872–1882). 3. Infectious myocarditis (1873–1888). 4. Toxic myocarditis (1891—). 5. Vagus degeneration (1893—). 6. Peripheral circulatory failure (1899—). 7. Conducting system degeneration (1910—).

In the analysis of this great mass of literature which has been contributed on the circulatory failure of diphtheria, one cannot help but feel that the final chaos is little more enlightening than the original state. Each investigator has championed one or other of the theories already enumerated and contributed his observations to strengthen this or refute that idea. So many carefully made investigations have been corroborated by competent observers, only to have amassed against them an array of contradictory evidence by equally skilled workers, that we approached the study of the circulatory failure of diphtheria with a view of attempting to combine the reliable data into one theory which would be supported by all of the existing evidence and refuted by none of it. If such a theory were possible, we desired then to attempt to add to its proof by further experimental and clinical data.

We were struck during our clinical observations by the fact that all cases of circulatory failure could be divided into two groups, one in which the collapse occurred at the height of the disease, the other when syncope and failure suddenly appeared to mar a seemingly uneventful recovery. In an analysis of 1600 consecutive cases of diphtheria admitted to the Sydenham Hospital from 1920 to 1927 there were 178 deaths. Of these 139 followed laryngeal diphtheria, in which the added factor of anoxemia, suffocation and resultant pneumonia so complicated the picture of pure diphtheria intoxication that they were not included for consideration. The remaining 39 were definite clinical cases of circulatory failure and were analyzed according to the day of the disease on which death occurred. Figure 1 is a graphic representation of the results. It is immediately striking that deaths in diphtheria fall into the two classes already mentioned—48 per cent occurring at the height of the disease from the 2nd to the 9th day after onset; the remaining 52 per cent falling between the 9th and 47th days when convalescence had apparently set in.

This fact has already been recognized by some clinicians, although as a rule it is used only to make a superficial classification of the cases into "late" and "early" heart failure. Thus Ker (8) mentions that "heart failure may occur early or late in the illness." Meara (9), however, calls attention to the fact that "one may distinguish an early and late form of circulatory disturbance" in cases of diphtheria but

gives no definite description. On the other hand, such authors as Welch and Schamberg (10), McClure (11), Goodhall (12) and Osler (13) make no mention of any such division and the investigators who have attacked the problem from an experimental standpoint have, for the most part, ignored it completely. These workers have made reliable observations on animals at the height of a diphtheria intoxication but have been unable to offer any explanation as to why these data were not supported by the clinical evidence of all cases of diphtheria. Clinicians who have advocated certain therapeutic measures in the treatment of circulatory failure of diphtheria have been at a loss to explain why consistent results were not obtained in all cases. We believe that the answer lies in the fact that the late and the early heart failure have a separate mechanism and etiology, so that data obtained in one are no more applicable to the other than therapeutic measures successful in the early cases can be relied on in the late ones. Working on this basis we have again reviewed the literature and attempted to classify the data according to whether they were applicable to early or to late heart failure, and to evolve therefrom a simple explanation of the mechanism of circulatory failure in diphtheria. We have added to this considerable supporting evidence resulting from our own experimental and clinical observations.

Clinical. It is obvious that circulatory disturbances occurring during the height of the disease in cases of diphtheria are due either directly or indirectly to the action of diphtheria toxin upon the circulatory system. This early type is therefore to be considered as an essential part of the disease entity. In any case of diphtheria, no matter how mild, the tissues of the circulatory system suffer under the action of the toxin just as all other tissues of the body are affected. Further evidence will be presented upon this point later.

Cases of early circulatory failure are therefore really the end stage of the disease, the result of a virulent infection and too often of neglect on the part of the parents to summon a physician until the condition has become alarming. Such patients present a piteous picture. They are apathetic and wish only to be left alone. The sensorium is clear but the sensibilities are dulled, as evidenced by the extreme quiet of the patients even in such an obviously uncomfortable condition, and by the unconcern with which they submit to the administration of

antitoxin or to venipuncture. The nose exudes a mucoid, hemorrhagic discharge containing large pieces of membrane, if the disease be of the nasal form. Or the throat may be almost occluded by large necrotic swollen tonsils covered by thick, white, grey, or even black membrane. The tonsillar region may be so swollen as to simulate a peritonsillar abscess; the neck glands may form a huge, painful collar, the so-called bull neck. A putrid, sickening odor emanates from such patients which is easily recognizable on entering the room. The temperature is always elevated; although it may be no higher than 100°, it usually ranges between 102° and 103°F.

The pulse is rapid and thready; the heart almost never enlarged. On auscultation, the sounds are surprisingly forceful and indicate the labored condition of the heart. The first sound is everywhere soft and blurred, the second loud and booming. A loud systolic murmur is usually present, best heard along the left sternal border, sometimes audible nowhere else. An enlarged and painful liver is one of the first signs of a failing circulation. As the toxemia progresses, there may develop a cardiac arrhythmia, at first simply an occasional premature beat with compensatory pause, later a total irregularity. At this stage, a protodiastolic gallop rhythm usually becomes manifest. This is the last stage of toxemia. Curiously enough, in cases of early circulatory failure the blood pressure remains normal or more often elevated until the last hour preceding death. This is contrary to general opinion, the hypotension so often found in late failure having overshadowed all cases of circulatory deficiency. Table I is a compilation of the blood pressure studies in several cases of early failure and illustrates this point.

As the toxemia progresses in these cases, the patients lapse rather suddenly into unconsciousness and die within an hour or so. The period of unconsciousness is practically identical with that during which the blood pressure is falling. The manner of death is usually quiet but sometimes it may be associated with convulsions.

Almost all cases of diphtheria present a systolic murmur at some time during the course of the disease. Osler (13) states that murmurs are found in 94 per cent of the cases and our own observations tend to confirm this. These murmurs usually appear toward the end of the first week and last from several days to months. In the more toxic

cases they may be noted from the start. Naturally enough, however, all of these cases may not present symptoms of definite circulatory failure and we include them in our classification only when the degree of toxemia and associated symptoms would warrent such an impression.

TABLE I

Blood pressure in cases of early circulatory failure of diphtheria

DAY OF DISEASE	BLOOD PRESSURE		REMARKS
	Systolic	Diastolic	
Case 11154. C. P., 8 years. Tonsillar and pharyngeal diphtheria			
5	120	70	Arrhythmia, systolic murmur, enlarged liver. Very toxic
6	120	70	Systolic murmur. Toxic
8	115	70	Systolic murmur. Improved
11	110	70	Systolic murmur. Very weak
15	105	60	Systolic murmur persists
33	110	60	Discharged. Condition good
Case 11141. A. M., 3 years. Nasal and tonsillar diphtheria			
6	100	75	Very toxic, systolic murmur, enlarged liver
7 2:00	100	75	Moribund
7 2:30	95	75	Dying
7 2:50			Died
Case 10803. H. L., 4 years. Nasal and pharyngeal diphtheria			
5	112	60	Arrhythmia, systolic murmur, gallop rhythm, enlarged liver. Very toxic
6	100	55	Systolic murmur, enlarged liver. Very ill
7	100	60	Improved. Systolic murmur
51	100	55	Discharged. Condition good

In contrast to this clinical picture are those cases which present what we have designated as the late circulatory failure. It must be borne in mind that this classification is not made primarily on the basis of the date of onset of the collapse as is that of most authors who have adopted this designation, but rather on the clinical picture presented. Cases of late circulatory failure in our series occurred as early as the eighth day of the disease, while death from early failure was noted as

late as the ninth. Yet the different clinical picture presented in each left little doubt as to its type.

Late circulatory failure occurs usually during the third week of the disease. Thus, in our series, collapse occurred earliest on the eighth day and as late as 47 days after the onset, with the average on the 18th day. This is usually at a time when the height of the illness is passed and the patient seems well on the way to recovery. The typical history is as follows: After the administration of antitoxin the temperature falls gradually to normal, the membrane sloughs and falls away and the patient begins to feel much improved. At times there may be a persistent tachycardia to point to a weakened circulatory system, but more often the pulse rate, too, returns to a normal figure. Then, after a week or more of apparent convalescence, the patient suddenly complains of mild abdominal pains and in a few hours begins vomiting, being unable to retain anything taken by mouth. He is quite conscious but usually very restless and uncomfortable. On examination, the heart may be found to be moderately dilated, although more often there is no enlargement demonstrable. The sounds are distant and soft, both the first and second sounds having a muffled quality. There is a marked arrhythmia, premature beats appear in abundance and a protodiastolic gallop rhythm may be evident. The arrhythmia is very apt to take the form of doublets or triads. The blood pressure is found somewhat lower than at its last reading just before the onset of the symptoms. The liver is markedly enlarged and tender to palpation.

This condition gradually becomes more severe and the patient becomes cyanotic and assumes a dusky hue. In most of these patients the temperature remains normal or else rises slightly just before death. The vomiting may stop but the patient continues to be restless and the blood pressure gradually falls. The diastolic pressure may fall so low that sounds are heard below the sphygmomanometer cuff with pressure gradients all the way down to zero.

Rarely the blood pressure rises slowly, the symptoms abate and the patient recovers. More often the condition becomes more serious, the patient lapses into unconsciousness and dies within an hour after. Very often the whole syndrome may be ushered in by a sudden fall in the pulse rate to 60, 40 or even 30 per minute. Such a bradycardia is

often seen in diphtheria and, while it should be viewed as a serious omen, many patients show only this symptom and ultimately recover completely.

Thus, tachycardia, bradycardia and simple pulse irregularities are common conditions in the late circulatory failure of diphtheria. In addition, we find a variety of other conditions, seen less often. Of these, we are able to recognize clinically complete heart block, auricular fibrillation and bundle branch block. All other types of disturbances such as auricular and ventricular premature beats, auricular

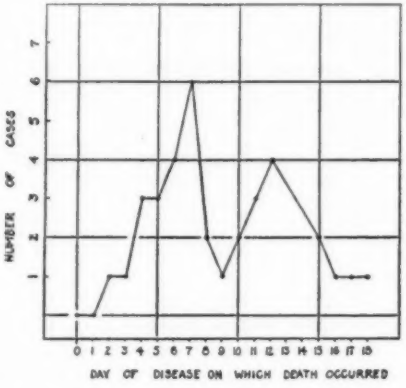

FIG. 1. SHOWING DISTRIBUTION OF FATAL CASES ACCORDING TO DAY OF ILLNESS ON WHICH DEATH OCCURRED

flutter, nodal premature beats, and others, are differentiated with the aid of the electrocardiograph. They form, however, a minor portion of the cases of late circulatory failure; indeed they are a rarity. Figures 2, 3, and 4 are graphic representations of the findings in three typical cases of late circulatory failure.

We feel, therefore, that all cases of circulatory failure of diphtheria may be differentiated into these two groups, early and late failure, on the basis of the clinical picture presented. Table 2 gives a comparison of these two types showing the main differences and similarities. That the division is further supported by existing data we shall at-

tempt to prove by a consideration of the pathology and experimental work on the subject.

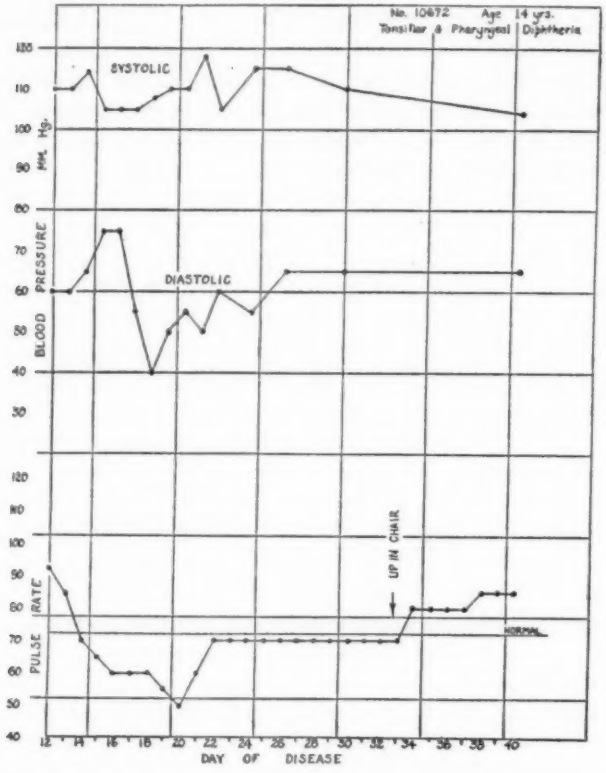

FIG. 2. CASE OF LATE CIRCULATORY FAILURE. BRADYCARDIA WITH NORMAL BLOOD PRESSURE

Pathology. There are still those who minimize the importance of the pathological changes found in the heart in diphtheria, but most workers are now agreed that it is impossible to ignore all of the pathological evidence which has been built up on this subject. Whether the changes found in the heart muscle are typical of diphtheria or

whether they are analogous to those found in any of the acute infectious diseases may be as yet undecided, but it cannot be denied that practically all cases of diphtheria show at autopsy certain changes in

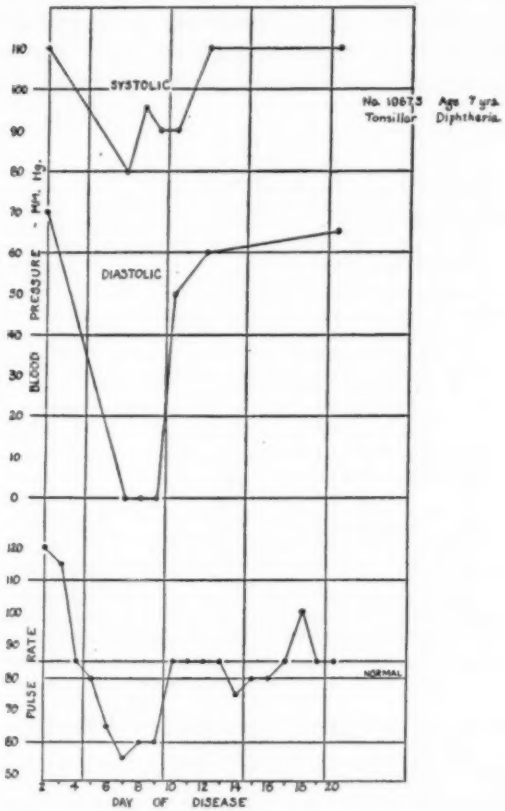

FIG. 3. CASE OF LATE CIRCULATORY FAILURE. BRADYCARDIA WITH HYPOTENSION

the myocardium. These have been extensively studied, notably by Councilman, Mallory and Pearce (14), Hecht (15), Anitschkow (16) and Heller (17). The findings of these workers are incorporated in a paper by Warthin (6). This is the latest work on the subject and his

findings are in entire agreement with those of the earlier writers; hence we shall limit our discussion to his paper. It is without doubt the most comprehensive study on the subject lately contributed and we have quarried from it extensively. Warthin states that the essential pathological lesion is a marked parenchymatous degeneration of the heart muscle, varying in degree with the severity of the process and with the stage of duration. In almost every case hyaline degeneration

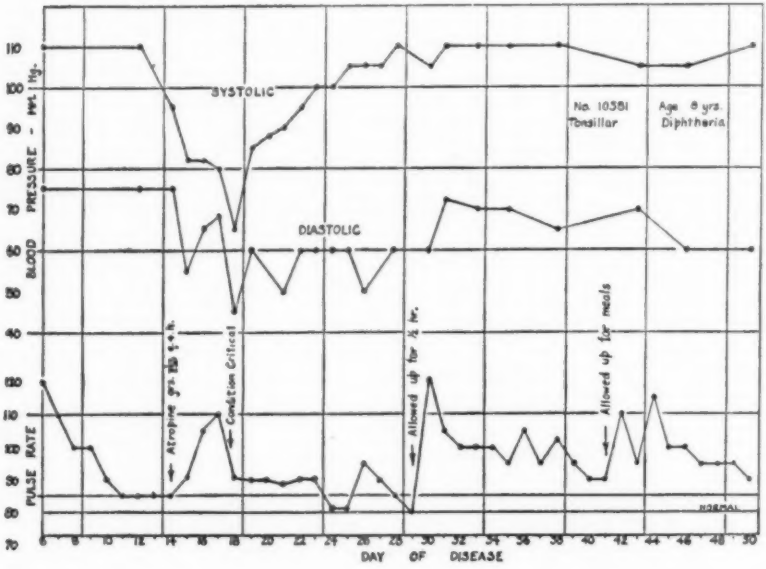

FIG. 4. CASE OF LATE CIRCULATORY FAILURE. HYPOTENSION WITH TACHYCARDIA

or necrosis is present. This is the one, practically constant parenchymatous lesion and is characterized by more or less tumefaction with loss of striation and staining power of the fibers. The nuclei may show little change in the early cases but are usually contracted, deformed and more or less pyknotic. In the more severe or prolonged cases the picture of a hyaline, waxy or typical Zenker's necrosis is present. Living portions of muscle may alternate with necrotic portions so that apparent gaps or defects occur in the fibers.

The hyaline change may be the only parenchymatous lesion present, or it may be associated with fatty degenerative infiltration or with cloudy swelling, or with both of these changes. Occasionally simple necrosis of individual fibers also occurs.

The His bundle shows the same type of pathological change as is seen in the muscle fibers, the degrees of degeneration running parallel. There is no evidence arguing for any special affinity of the toxin for the conducting system.

TABLE II

Comparison of early and late types of circulatory failure of diphtheria

EARLY CIRCULATORY FAILURE	LATE CIRCULATORY FAILURE
Onset 2nd to 9th day	Onset 7th to 50th day
Onset gradual	Onset sudden
Previous course progressively downhill	Previous course usually convalescent
Patient quiet	Patient restless
Temperature elevated	Temperature normal
Vomiting rare	Vomiting usual
Abdominal pain seldom	Abdominal pain usual
Liver enlarged often	Liver usually enlarged
No cardiac enlargement	Cardiac dilatation often
Tachycardia	Tachycardia or bradycardia
Heart sounds loud	Heart sounds soft
Arrhythmia terminal	Arrhythmia usual and introductory
Normal blood pressure	Progressive hypotension
Conducting system symptoms seldom seen	Conducting system symptoms often seen
Protodiastolic gallop, terminal	Protodiastolic gallop usual
Electrocardiogram normal	Electrocardiogram abnormal
Recovery of cardiac reserve always complete	Recovery of cardiac reserve usually complete

In patients who died late in the disease Warthin (6) found, in addition to the above changes, the same type of regenerative process previously described by Heller (17) and Anitschkow (16). This consists of a lymphocytic and polymorphonuclear infiltration about the small vessels in the stroma of the damaged portions of the muscle. As the interstitial edema increases, the picture of Zenker's necrosis with vacuolation, or of simple hydropic degeneration alone appears. The muscle fibers become fragmented or frayed, partly liquefied and absorbed. Plasma cells and fibroblasts appear in the stroma; the pic-

ture of a well developed myocarditis results. This is apparently wholly reparative in nature, however. Near the necrotic or degenerated portions of the heart muscle, the nuclei of the muscle show a great variety in size and form. They increase in length and show many evidences of longitudinal splitting in every possible stage of such a division. The living muscle substance bordering on the injured area also undergoes longitudinal splitting into muscle bands containing these nuclei; these bands grow into the perimysial tubes, filling them up, replacing the cell detritus and connecting with the living muscle on the other side of the defect. Thus the defects in the muscle caused by hyaline necrosis may be ultimately bridged by a number of new muscle bands.

With the regeneration of the heart muscle there takes place a parallel proliferation of the stroma. To what extent the newly formed connective tissue persists in the form of localized fibrosis, or whether the proliferation of the stroma is necessary only as a congenial environment for the development of the new muscle fibers bridging the defects, has not been decided.

Patients who died late in the disease showed in the bundle of His the same interstitial edema and vacuolation of the fibers with round-cell infiltration as was seen elsewhere.

Thus, it may be seen that the pathologists are struck by two types of lesions found in the myocardium following death from diphtheria. The first is a toxic parenchymatous hyaline degeneration found early in the disease, the other a reparative inflammatory process (myocarditis) accompanied by muscle regeneration which usually appears toward the end of the second week. If, now, we review the protocols of the cases studied by Warthin (6) in the light of the clinical pictures we have already described for early and late circulatory failure, we find that twelve of his cases (1, 4, 5, 6, 7, 9, 10, 12, 13, 14, 15, 16) fall into the classification of early failure and the remaining four (Cases 2, 3, 8, 11) may be recognized as late circulatory failure. It is significant that the time of death in these cases is divided as follows: Early failure, 2, 2, 2, 2, 3, 4, 4, 5, 6, 12, 14 and 15 days; late failure, 13, 21, 21, 42 days. It is still more significant that of the twelve cases classed as early failure from the clinical picture, ten showed the parenchymatous degenerative lesions alone, the other two showed in addition only

a beginning cellular infiltration. Of the four cases classed as late failure, three showed well marked cellular infiltration and repair. Curiously enough, the fourth case failed to show this.

We believe, therefore, that this evidence points to two distinct mechanisms underlying the early and late circulatory failure of this disease. Thus, in any case of diphtheria, the toxin acts upon all tissues and causes degenerative reactions. The statement so often made, that it has an especial affinity for the highly specialized tissues, we believe not to be supported by existing evidence. It would seem natural for degenerative processes in highly specialized tissues, such as nerves and heart muscle, to cause symptoms much earlier than equivalent lesions in less specialized tissues. Warthin (6) found lesions in the striped muscles and nerve trunks identical with those found in the heart muscle.

As the toxemia progresses, the degenerative process in heart muscle, conducting system, vagus nerve, vaso-motor centers and arterial and arteriolar muscle fibers advances. Finally, any one or more of these becomes incapable of maintaining its burden and symptoms of fibers circulatory failure develop. Most commonly the heart muscle fibers fail first and irregularities of pulse appear, the liver becomes engorged and general symptoms of myocardial insufficiency are presented. Late in the toxemia the blood pressure falls; it seems quite probable that failure of the muscular elements of the arterioles to maintain their tone may be as much to blame as the hypotension incident on the badly damaged myocardium. Rarely the conducting system itself is first to suffer a break and such disturbances as heart block, auricular fibrillation, etc., may become apparent. (Marvin (7)). These are, however, rarely seen in cases of early circulatory failure and when they do occur are almost always the end stage. If the intoxication progresses, of course, the failure of any one or of any combination of these systems may become so great as to be incompatible with life. Patients dying in this stage show only the parenchymatous degeneration of the muscle fibers and the His bundle already described. If, however, the toxemia is not overwhelming, the symptoms begin to abate and the patient starts convalescence. An attempt is then made by the body to repair the damaged areas. The dead portions of the muscle act as a foreign substance stimulating phagocytosis by leucocytes and the pro-

duction of foreign-body giant cells in the stroma. The perimysial tubes become filled with detritus and cells, at first chiefly polymorphonuclear leucocytes, later with a variety of forms, fibroblastic and myoblastic. It is our opinion that the phagocytosis and absorption of the injured muscle fibers, chemically altered by their combination with the diphtheria toxin, sets up localized reactions and increases the cellular infiltration, and areas of localized myocarditis develop about the in-

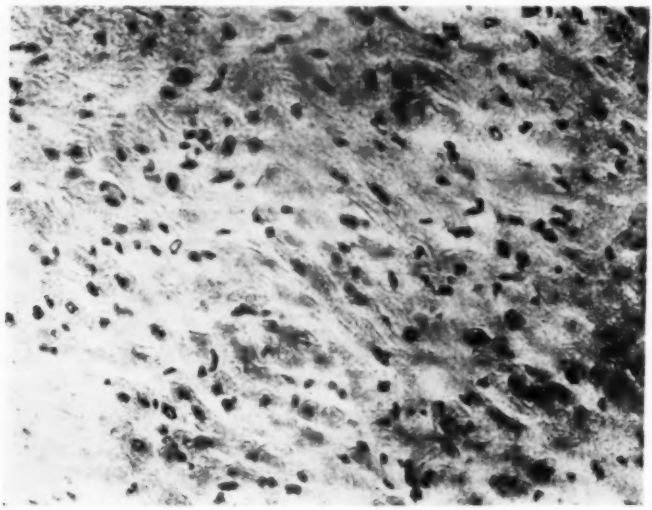

FIG. 5. MYOCARDIUM IN CASE OF EARLY CIRCULATORY FAILURE, THREE DAYS' DURATION. AREA SHOWING HYALINE DEGENERATION BUT NO INFLAMMATORY REACTION (WARTHIN)

jured portions of the myocardium. This view is supported by the dense cellular infiltration and interstitial edema seen about the injured areas and extending far back into the uninjured portion (Figs. 5 and 6). As these areas of localized inflammation encroach upon the portions of living muscle, which nevertheless must have been injured to some extent by the diphtheria toxin, the degree of injury is increased, the efficiency of more and more muscle fibers is lowered until finally the limit of cardiac reserve is reached and the symptoms of

definite myocardial failure appear. We also believe that there may be added to the insult to the surrounding muscle of this localized inflammation, the contractile inefficiency of thousands of muscle fibers seen in active stages of longitudinal splitting and division. All of the pathological changes just described are seen late in the disease, in patients dying of late circulatory failure. We believe, therefore,

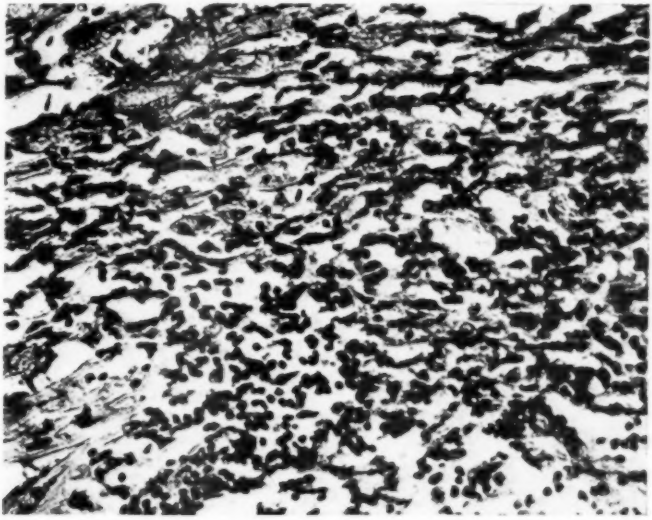

FIG. 6. AREA IN MYOCARDIUM OF CASE OF LATE CIRCULATORY FAILURE, FIFTEEN DAYS' DURATION, SHOWING WIDESPREAD INFLAMMATORY REACTION AND AREAS OF DESTRUCTION OF THE MUSCLE FIBERS (MARVIN)

that they are not due directly to the action of the diphtheria toxin but are rather the result of the process of repair.

The same changes seen in the myocardium are seen in the conducting system and vagus nerve, and it is our view that the sudden breaks in conduction seen in late circulatory failure are due to this same reparative inflammatory reaction. The failure of the various parts of the circulatory system may occur in any possible combinations and thus give rise to the varied conditions seen in this form of circulatory failure of diphtheria.

If the cardiac embarrassment has not been sufficient to cause death the regeneration of the damaged portions continues, usually with complete replacement of the original tissue. In such cases there is no resultant cardiac weakness. Clinical evidence points to the fact that by far the greater number of patients recovering from circulatory failure in diphtheria are able to meet fully the demands of an active life. Occasionally, fibrosis of various portions occurs, and if such lesions are unfortunately placed, permanent cardiac damage results. Thus, one of our patients has continued to show right ventricular extrasystoles to date, eight months after his attack, although his cardiac reserve seems good. Another patient, whose history we have studied, maintained a delayed conduction rate (PR interval = 0.26 second) and finally died in one of the attacks of fainting and syncope to which he was subject.

Electrocardiographic. Confirmatory evidence for our views as to the classification and mechanism of circulatory failure in diphtheria is also to be found in electrocardiographic studies. The most important of the later works on this phase are those by Marvin (7), Smith (18) and Nathanson (19). Smith made electrocardiographic studies on 242 patients suffering from diphtheria and concluded that the heart abnormalities are manifest in disturbances of the conduction system and may be divided into (1) initial tachycardia accompanying the appearance of the diphtheritic membrane and usually subsiding within forty-eight hours following the administration of antitoxin, and (2) irregularities of pulse in convalescence, appearing 6 to 8 days after subsidence of the initial tachycardia. Of these convalescent abnormalities, 65 per cent consist of sinus arrhythmia and a condition called sino-auricular block; 20 per cent consist of premature contractions. None of the three are accompanied by signs of circulatory embarrassment. The remaining 15 per cent, however, consist of high-grade heart block accompanied by grave symptoms and usually resulting in death.

Nathanson (19) also studied cases of diphtheria during convalescence and found that 50 per cent showed inversion of the T wave. He considers this of serious import and concludes that it represents an expression of an abnormal dying away of the excitation process.

Marvin (7) studied 90 cases of diphtheria in all stages of the disease,

in 10 of which death occurred from circulatory failure. We have therefore reviewed these cases in the light of our present classification of circulatory failure and find that four patients died of symptoms typical of the early type (Cases 4, 5, 9, 10). The remaining 6 cases (1, 2, 3, 6, 7, 8) are examples of late circulatory failure. Although Marvin found disturbances in auriculo-ventricular and intraventricular conduction in all of these cases, we believe it to be significant that, in those which we classified clinically as early failure, marked changes in the electrocardiographic records were not noted until a few hours before death. On the other hand, the cases grouped as late failure showed definite changes from 1 to 15 days before death. This is in agreement with our clinical observations. In cases of early failure, cardiac symptoms, especially conduction changes and irregularities, usually appear only when the toxic process has progressed so far as to make death imminent. In cases of late failure, however, such symptoms are the first sign of a failing circulation and may persist for several days before death.

SUMMARY

We have presented evidence which we believe allows of a classification of the circulatory failures of diphtheria into two groups, early and late, on the basis of the clinical symptoms and picture presented. This classification is not to be confused with that sometimes found in the literature where "early" and "late" signify simply the time of onset. We feel that cases of early circulatory failure are an essential part of the diphtheria intoxication, and to be treated accordingly. The late circulatory failure, however, is a complication of the disease caused probably by local inflammatory reactions incident to regeneration and repair. A further communication on the treatment of circulatory failure in diphtheria will be presented later.

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ERRORS OF REFRACTION, AGE AND SEX IN RELATION TO THE SIZE OF THE FORM FIELD AND PRELIMINARY DATA FOR A DIAGNOSTIC SCALE

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INTRODUCTION

The present study is one of a series on eye diseases in relation to test results. The work will proceed along two lines: (1) A large number of nonpathological cases will be studied for the purpose of knowing the range and distribution of results for such cases. Without this knowledge a satisfactory degree of certainty in the separation of nonpathological from pathological cases on the basis of test results is impossible. And (2) pathological cases will be studied for their characteristic and differential features. Both experimental and statistical methods will be used. It is our hope in these studies to create a definite, understandable and teachable literature on the subject.

Before such a program can be carried out, however, a great deal of preliminary work must be done in the selection and devising of tests and in giving them the sensitivity that is needed to pick up small differences and changes in pathological conditions and the precision that is required to give a satisfactory reproducibility of result. Some of the work on the revision and refinement of test procedure has already been done; the remainder will be completed as the work proceeds. Important fields of application are perimetry and other types of study of the visual field.

During the past several years papers have been published by two of the present writers showing the effect of variable factors on the size and shape of the form and color fields and describing the apparatus and controls which are needed to eliminate or minimize the effect of these factors and to secure accuracy and precision of result in perim-

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etry. The work reported in these studies, however, constitutes only a part of the program which is needed to make perimetry serve a widely useful purpose. A means has yet to be provided for adapting the type of perimetry described to the work of the office and clinic and other fields of application. The present paper is the first of a series designed to carry out this purpose. The work reported in this paper is intended to serve the double purpose of determining the effect of errors of refraction,[3] age and sex, on the size and shape of the form field and of collecting preliminary data to serve as a nucleus for a diagnostic scale.

The determination of the form field has two important clinic uses: a study of the advance or recession of a given pathological condition, and diagnosis. Both of these uses demand a high precision of working and a careful control of the variable factors which may influence the result. This precision has been attained within a very small limit of error in so far as the reproduction of the results for a given individual is concerned. The study of the individual case, therefore, can be carried on with a degree of accuracy comparable with the most highly developed types of laboratory testing. In diagnosis, however, we have to deal not only with the factors which may cause a variation in result from time to time in an individual but also with those which differ from individual to individual. These latter factors are being studied at the present time, but the work is not yet completed. Some of them may be amenable to control; the greater number, however, in all probability can not be controlled by any procedure which would be feasible for practical work. Two of them at least must always remain outstanding: the normal variations in the sensitivity of the retina and in the distribution of sensitivity over the retina. A highly necessary first step, therefore, towards the successful use of either the form or color fields for diagnosis is the determination of the range of variation which may be expected for nonpathological cases. This determination of a norm for the nonpathological cases and the normal range of variation from an average or median result is obviously even more necessary for the successul practice of perimetry than the analo-

[3] By errors of refraction are meant here errors in central field refraction. We have been able as yet to take into account refraction for the peripheral field only in detailed individual studies.

gous determinations for acuity, for example. In neither case, however, have determinations been made with regard to both of the features indicated above; nor with regard to either with an adequate standardization of factors. In these respects the work in perimetry in particular has been greatly neglected. To make such determinations effective for the practice of perimetry the following are some of the conditions which must be fulfilled.

(1) They must be made under a prescribed set of conditions which can be widely reproduced. Until the necessity of this constancy of conditions is thoroughly understood any plan for calibrating a scale for diagnostic purposes must fail. The wide differences in result which are obtained when care is not taken to control the conditions under which the fields are determined have been shown in previous papers.[4] An obvious requirement for the validity of application of any scheme of calibration is that the scale which is determined shall be applied only to results obtained under the same conditions as those for which the scale was made.

(2) The results must be treated in such a way as to show the range and distribution of cases as well as the average case. Previous writers on this subject seem to have been content to give the breadth of field in the principal meridians for the average case, or at most only a small range of variation on either side. The knowledge of what is an average field obviously contributes but little to the diagnosis of the cases for which the help of perimetry is most needed. If a pathological condition is to be diagnosed in its incipiency, the borderline between normal and pathological conditions must be located within reasonably narrow limits. For example, a given field may be much smaller than the average and still fall within the range of normal variation. An adequate scheme of calibration of perimetry for diagnosis should consist,

[4] Ferree, C. E., and Rand, G. Factors which influence the color sensitivity of the peripheral retina. *Trans. Amer. Ophthal.*, 1920, **18,** 171–197; The effect of variations of the intensity of illumination of the perimeter arm on the determination of the color fields. *Psych. Rev.*, 1922, **29,** 457–473; Effect of brightness of pre-exposure and surrounding field on breadth and shape of the color fields for stimuli of different sizes. *Amer. Jour. Ophthal.*, 1924, **7,** 843–850; Effect of size of stimulus on size and shape of color fields. *Amer. Jour. Ophthal.*, 1927, **10,** 399–411.

therefore, of a scale made of two frequency curves, one for the nonpathological, the other for the pathological cases. As the work progresses, it may be found advisable to make a scale for each of the pathological conditions considered separately. In each of these scales the cases should be grouped with reference to size of field along the same coordinate. Such scales provide a means of placing any new case in the class or group to which it belongs, rated with regard to size of field. In obtaining the data for the nonpathological plot the cases should be sampled broadly to include as many as possible of the outstanding variables. The present determinations which represent only the beginning of the work have been made to include two of the most important of these variables, namely, age and condition of refraction. The data and range of conditions covered will be increased as opportunity offers.[5] The data for pathological cases will not be dealt with in this paper.

If extent as well as shape of field is to be used as a diagnostic feature, some accurate means of comparing extents must be had. The means employed at present seems to be a comparison of width of field in the different meridians or an inspection of the plotted fields. Neither of these methods is convenient and in many cases they lead to no definite conclusion. Some fields may be broader in certain meridians and narrower in others than another field or any field or range of fields accepted as a standard. The need of a single value or index which will fairly represent the extent of the field is obvious. One solution of this problem is to plot the field to a standard scale and measure its area with a planimeter. This would be the customary scientific procedure. It would necessitate, however, that the fields always be plotted to a standard scale or the results be corrected to that scale, and would require, besides, the use of an instrument which may not always be included in the equipment of the examiner. For these reasons it has been deemed advisable to find an alternative plan of treating the results which can be used when desired as a substitute for planimetry. A number of methods have been tried and the results

[5] It is obvious that the scale presented in this paper may be filled out by any worker in this field from the cases which he may be called upon to examine. With 200 cases as a nucleus a scale can soon be formed which will serve a very useful purpose in diagnosis.

checked against those obtained with the planimeter to see which gives the closest agreement. Fortunately, a very simple method was found which gives a very high correlation with the results obtained with the planimeter. In this method the grouping was based on an average value computed by adding together the distances of the limit in degrees from the center of the field in the several meridians as read from the arc of the perimeter and dividing this sum by the number of meridians in which the determinations were made.[6] This result may, for convenience, be called the average breadth of the field. With regard to this comparison it is only fair to state, however, that the rankings given to the fields by the two methods were not always the same. In such a case it is not easy to decide which method should be used nor, quite aside from considerations of convenience and serviceability, is it easy to say which more correctly represents the range of distribution of sensitivity over the retina when the limits are determined only in a comparatively small number of meridians. Obviously, either method might be adopted for the purpose of determining norms and of making comparisons with these norms for diagnostic purposes. Results for both methods have been included in this paper.

CON ITIONS UNDER WHICH THE FIELDS WERE TAKEN

The experimental work was done on the Ferree-Rand perimeter.[7] This perimeter was designed for the control of all the variable factors

[6] As in former papers, the term meridian is used here for the quadrant of the meridian. While it is not necessary in refraction to treat the two anterior quadrants of the meridian separately, there is an important need for the separate treatment in perimetry.

Since the situation and needs in perimetry and refraction are so different, there seems intrinsically to be no good reason why the same designation should be used in the two cases. It might be advisable and convenient in perimetry to adopt the term *quadrant* and to number the quadrants for the right eye counter-clockwise from 0, right horizontal, to but not including 360°; and for the left eye clockwise from 0, left horizontal, to but not including 360°. By this method the quadrant designations would correspond throughout for the two eyes, *i.e.*, 45° would represent upper temporal, 135° upper nasal, etc. for both eyes; but two sets of maps would be required, one for the right eye and one for the left. Similarly two concentric sets of graduations would be needed on the dial of the perimeter.

[7] Ferree, C. E., and Rand, G. A new laboratory and clinic perimeter. *Jour. Exper. Psychol.*, 1922, **5**, 46–67.

which affect the determination of the form and color fields for a given eye. Among the special features and devices of this perimeter, the following may be reviewed here: a means of illuminating the perimeter arc such that every point on the arc in any meridian in which it may be placed receives light of equal intensity and of daylight quality; a means of controlling the brightness of the preexposure and the surrounding field; devices and adjustments for the accurate location of the eye at the center of the perimetric system and for securing a steady and precise control of fixation; special fixation controls for eyes suffering from presbyopia, high degrees of hyperopia, myopia, low central acuity and central scotomata; attachments for studying the blind spot and for refracting the peripheral field; a tangent screen or campimeter attachment, subtending a visual angle of 70°, every point on the surface of which can be given approximately equal illumination and with which all of the fixation devices noted above can be used, etc. With such an instrument all of the external conditions of the test can be held constant and be reproduced at will. The fields were determined with a white stimulus on a black background. The coefficients of reflection of stimulus and background were respectively 78 and 4 per cent. The angle subtended at the eye by the stimulus was 1 degree. The illumination of the stimulus at every point in the field was kept constant at 7 foot-candles. The cases examined include private patients, doctors, nurses, assistants on the hospital staff and a large number of clinic patients. In every instance the refractive condition of the eye was determined and an ophthalmoscopic examination was made. No case showing a pathological condition, however slight, was included in the present series. Ample rest periods were allowed between observations, and care was exercised that no field should be taken when the observer was suffering from general fatigue or was otherwise unfit for accurate work. All determinations were carefully checked but the observer was not given extensive preliminary training. It was not the purpose of the writers to make examination for the determination of norms under conditions differing in this respect from those which obtain in the ordinary practice of perimetry. The results obtained are, therefore, a fair sample of the fields that may be expected in an average group of untrained observers who show no pathological condition.

RESULTS

Fields were determined in 8 meridians (0, 45, 90, 135, 180, 225, 270 and 315 degrees) for 200 eyes. The eyes examined included 75 cases of hyperopia and hyperopic astigmatism; 30 cases of myopia and myopic astigmatism; 40 cases of presbyopia; 5 cases of mixed astigmatism; and 50 cases showing no error of refraction or an error no greater than 1 diopter or hyperopia or a quarter diopter of hyperopic astigmatism. This latter group contained no cases of myopia or myopic astigmatism. For convenience of treatment it will be referred to as emmetropic. The observers ranged in age from 8 to 56 years. There were 84 males and 116 females.

Graphic representations of the results are given in Figures 1–3. In Figure 1 the cases are rated on the basis of average breadth of field in the 8 meridians, expressed in degrees. The total range of average breadth of field for the 200 cases was from 59.9 to 74.4 degrees. For the purpose of grading and representation in the plot the cases were separated into 9 groups, each group covering a range of 2 degrees. The number of cases falling in each group is shown on the vertical coördinate. The cases are designated with regard to condition of refraction according to a key shown in the chart.

The results represented in Figure 1 may be summarized as follows:

(1) In general the emmetropes and hyperopes have the wider fields; the myopes and presbyopes the narrower fields.

(2) Ranked from narrowest to widest, the percentage of cases falling in each of the 9 groups is as follows: 0.5, 4.5, 12.5, 24, 32, 15.5, 8, 2.5 and 0.5.

(3) The myopes constitute all of the first group, 44.4 per cent of the second group; 28 per cent of the third group; 8 per cent of the fourth group; 14.5 per cent of the fifth group; 9.7 per cent of the sixth group; 6.2 per cent of the seventh group; 20 per cent of the eighth group, and none of the ninth group. The presbyopes form no part of the first, seventh, eighth and ninth groups; 33.3 per cent of the second group; 52 per cent of the third group; 25 per cent of the fourth groups; 14.5 per cent of the fifth group and 6.5 per cent of the sixth group. Emmetropes are not found in the first, second and ninth groups; they form 12 per cent of the third group; 23 per cent of the fourth group; 22.6 per

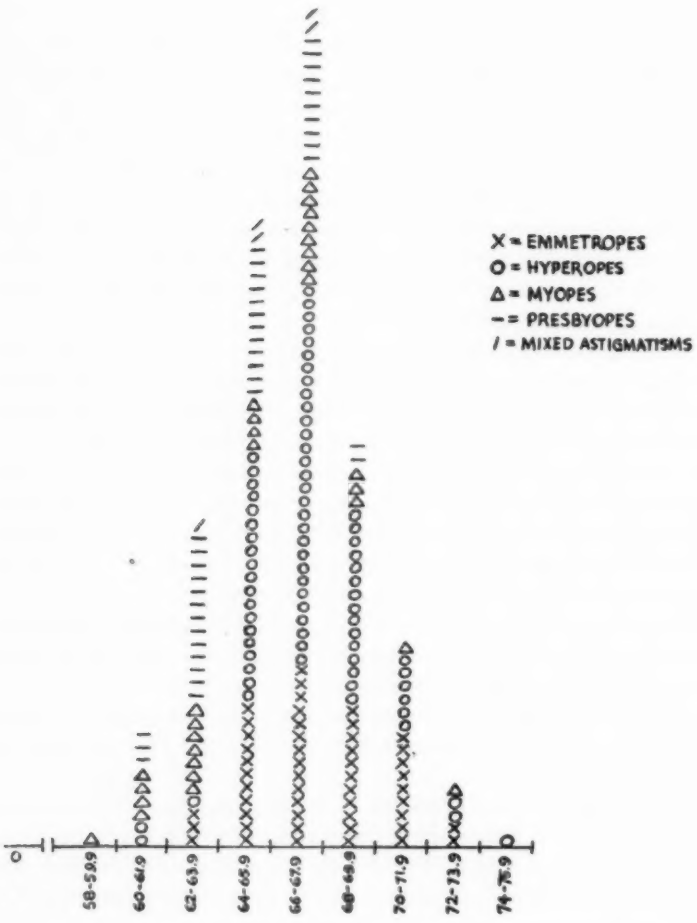

FIG. 1. SHOWING THE DISTRIBUTION OF 200 NONPATHOLOGICAL CASES

The observers were selected to include cases of emmetropia, hyperopia, myopia, presbyopia and mixed astigmatism. The distribution is based on the average breadth of field in the eight principal meridians. Breadth of field in degrees is plotted on the horizontal coördinate and number of cases on the vertical coördinate.

cent of the fifth group; 35.5 per cent of the sixth group; 56.2 per cent of the seventh group; and 40 per cent of the eighth group. No hyperopes are found in the first group; they form 22.2 per cent of the second group; 4 per cent of the third group; 39.6 per cent of the fourth group; 46.8 per cent of the fifth group; 48.4 per cent of the sixth group; 37.5 per cent of the eighth group; and all of the ninth group.

(4) The distribution of average breadth of field for the entire group of 200 cases, it is interesting to note, is of the type frequently found

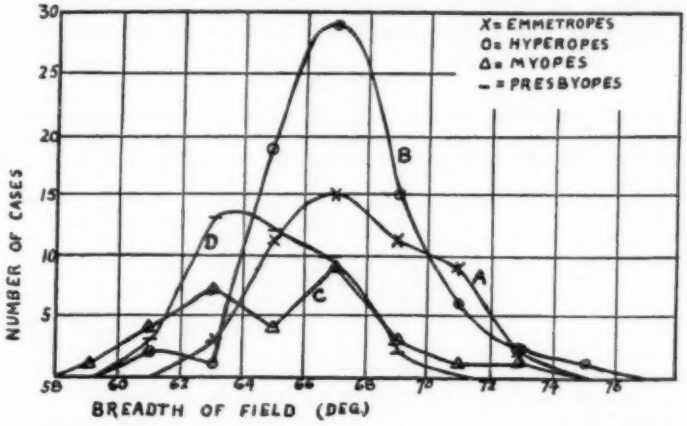

FIG. 2. SHOWING THE DISTRIBUTION OF THE 200 NONPATHOLOGICAL CASES FOR EACH REFRACTION GROUP: *A*, EMMETROPES; *B*, HYPEROPES; *C*, MYOPES D, PRESBYOPES

The distributions are based on average breadth of field in the eight principal meridians. Breadth of field in degrees is plotted on the horizontal coördinate and number of cases on the vertical coördinate.

when a large number of measurements is made of some physiological characteristic. That is, the bulk of the cases cluster around a median value, fewer and fewer occurring as this value is receded from. Whether or not the frequency distributions of field size for nonpathological cases will be found to fit the normal or Gaussian curve, as many other physiological traits have been found to do, can not be determined until a much larger number of cases has been investigated. The approximation is as close as can be expected, however, with 200 cases.

In Figure 2 is given a graphic representation of the distribution of results for each refraction group considered separately.

In the consideration of these graphs the question of causes of relation of error of refraction and size of field naturally arises. The following possibilities are suggested: (*a*) Unclearness of the image in the more extreme cases of refraction defects. The consideration of this possibility is complicated, however, by the lack of knowledge for the cases in question of the refraction situation for the peripheral portions of the field. In our more detailed and scientific work in the study of the peripheral field we have been accustomed to determine its refrac-

TABLE I

Showing for the entire group of 200 nonpathological cases and, for each refraction group, the average value of average breadth of form field, the standard deviation (σ), the coefficient of variability ($100\ \sigma/M$), the range for all cases in each group, and the range for the middle 50 per cent of cases

GROUP	AVERAGE VALUE OF AVERAGE BREADTH OF FORM FIELD (DEG.)	σ	$100\ \sigma/M$	RANGE OF SIZE OF FIELD					
				Total number of cases			Middle 50 per cent of cases		
				Limiting values	Degrees	Per cent	Limiting values	Degrees	Per cent
Entire group (200 cases).....	66.45	2.62	3.9	74.4–59.9	14.5	24	68.1–64.6	3.5	5
Emmetropes (50 cases).....	67.59	2.56	3.8	73.0–62.9	10.1	15	69.8–65.3	4.5	7
Hyperopes (75 cases).....	67.1	2.57	3.8	74.4–60.6	13.8	20	68.3–65.6	2.7	4
Myopes (30 cases).....	65.14	3.10	4.8	72.0–59.9	12.1	19	67.0–62.9	4.1	6
Presbyopes (40 cases).....	64.85	2.14	3.3	69.1–61.0	8.1	13	66.1–63.3	2.8	4

tion. In a study of the kind made here such a detailed specification of condition of refraction was quite impossible. (*b*) The placement of the image on the retina. For example, in cases of hyperopia due to deficient curvature of the cornea one might expect as a phenomenon of refraction that the image for a given excentricity of stimulus in the field would be formed nearer to the center of the retina than for the same position of the stimulus in cases of emmetropia and myopia. The tendency of this factor would be to widen the field for hyperopia. Conversely, in cases of myopia due to excessive curvature of the cornea, one might expect for a given excentricity of the stimulus in the field that the image would be formed relatively farther from the

center of the retina. The influence of this factor would tend to narrow the field in myopia. (*c*) Characteristic differences in shape of eyeball, in the degree of development and sensitivity of the nervous structure and in the health of the eye. And (*d*) age as a dominant factor

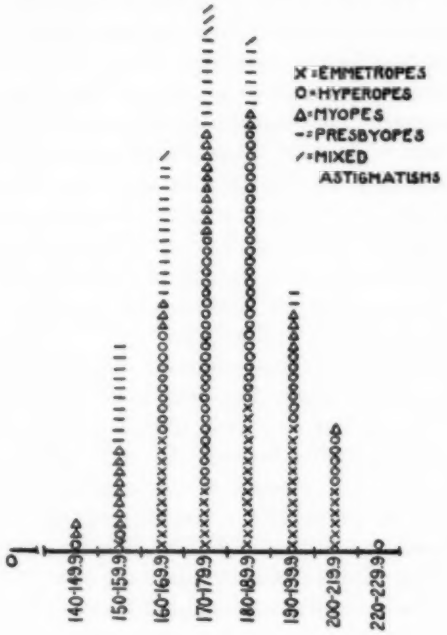

FIG. 3. SHOWING THE DISTRIBUTION OF 200 NONPATHOLOGICAL CASES

The distribution is based on area of field as measured with a planimeter from maps drawn to a scale of 10 degrees to 12 mm. Area of field in square centimeters is plotted on the horizontal coördinate and number of cases on the vertical coordinate.

in presbyopia. With the exception of (*d*) the data presented in the paper do not justify any serious attempt at a differential evaluation of the possibilities suggested. It may be noted, however, that the sizes of field obtained in the greater number of cases of hyperopia and myopia are in the direction that might be expected from the factor, curvature of cornea.

Table I shows for the entire group of 200 cases and for the different refraction groups, the average value of average breadth of field, the standard deviation (σ), the coefficient of variability (100 σ/M), the range for each group, and the range for the middle 50 per cent of cases in each group. It is seen in this table that the averages are larger for the emmetropic and hyperopic groups; and the scatter is greatest for the myopic and least for the presbyopic group.

In Figure 3 the results are shown in terms of area of field as measured with the planimeter. The maps measured were drawn to a scale of 10 degrees to 12 mm. The total range of area in square centimeters for the 200 cases was from 144.7 to 222.8 sq. cm. For this plot the cases were separated into 8 groups, each group covering a range of 10 sq. mm. The number of cases in each group is represented on the vertical coördinate; the range of the group in square millimeters on the horizontal. The condition of refraction of the cases is designated according to the key given in the chart.

Our strongest interest in these results is, of course, their diagnostic serviceability. In discussing diagnostic possibilities, the fact must be recognized that in this, as in most physiological studies, it will be difficult to draw a sharp line between the pathological and nonpathological cases. A certain amount of overlapping is to be expected. There will be in all probability a borderline group whose status is doubtful. Indeed one of the chief incentives for refining a test for diagnostic purposes is the desire to reduce the number of cases which must be classed as borderline. Although 200 cases are a small number from which to generalize or to form a diagnostic scale, there are a few conclusions which may be drawn from the results obtained with a fair degree of confidence. An examination of Figure 1 shows, for example, that there is only one case whose average breadth of field is less than 60 degrees. It may be safely concluded, therefore, that any field which has an average breadth of less than 60 degrees must be regarded as suspicious. It will be noted also that there are only six cases of emmetropia and hyperopia for which the average breadth of field falls below 64 degrees. This would seem to justify the conclusion that emmetropes or hyperopes with an average breadth of field less than 64 degrees should be classed as doubtful. Probably we can add that a myope or presbyope having an average breadth of field below

62 degrees falls within the doubtful class. The differentiation here, however, is not so clean-cut and incisive as in the other cases. In later papers not only will the data given here for the nonpathological cases be increased, but comparisons will be made with a large group

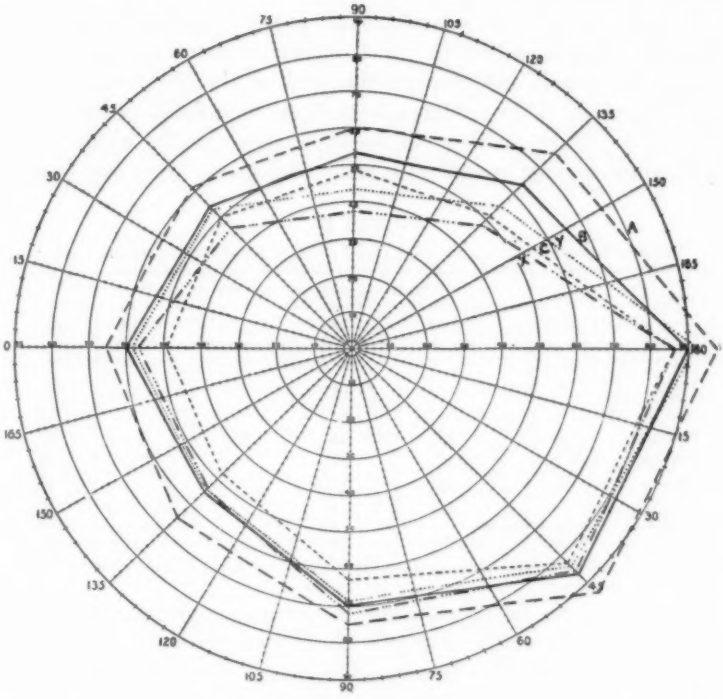

FIG. 4. SHOWING THE WIDEST FIELD, *A*, FOR 200 NONPATHOLOGICAL CASES; THE AVERAGE FIELD, *B*; THE NARROWEST FIELD, *C*; AND THE SIZES OF FIELD WHICH MAY BE REGARDED AS BORDERLINE, *X* FOR MYOPES AND *Y* FOR EMMETROPES AND HYPEROPES

of pathological cases in order to give a better understanding of the extent to which overlapping may be expected. In this connection, it should be remembered that we are dealing here with only the more difficult and discouraging aspect of diagnosis by means of the form

field, namely, size of field. Changes in the shape of the field are in general much less difficult to evaluate, partly because of the kind of change which is apt to take place as the result of a pathological condition and partly because of the smaller normal variation in shape as compared with size.

In Figure 4, fields have been plotted to show graphically the more important facts noted above. In this map are given the largest field found, the smallest field, the average field for the 200 cases, and the outer boundary of the two groups which we have called borderline or suspicious. Of these latter two fields, X represents the widest of the fields whose average breadth falls below 62 degrees. Any field smaller

TABLE II

Showing the number of cases in each group of size of form field for each age group

AGE	AVERAGE BREADTH OF FORM FIELD (DEG.)					
	58–61.9	62–65.9	66–69.9	70–73.9	74–77.9	Total
years						
0–9			1			1
10–19		14	28	5		47
20–29	4	19	36	12	1	72
30–39	2	10	17	4		33
40–49	4	16	10			30
50–59		14	3			17
Total.....	10	73	95	21	1	200

than this we have called suspicious for myopes or presbyopes. Field Y represents the widest of the six cases of emmetropia or hyperopia whose average breadth is less than 64 degrees. Fields for emmetropes or hyperopes smaller than this we would regard as suspicious. An inspection of this map should give a good idea within what limits a field should fall to be within the normal range of variation.

Tables II and III have been compiled to show the relation between age and average breadth of form field in the eight principal meridians. The range of size of field is treated in 5 groups of 4 degrees each, the range of age in years in 6 groups of 10 years each. The rows of Table II show the frequency of occurrence of each group of size of field for each age group; the columns, the frequency of occurrence of each age

group for each size of field. In Table III is shown the percentage of occurrence of each group of size of field for each age group.

An inspection of these tables shows that there is some tendency for size of field and age to vary concomitantly, the larger fields occurring at the younger ages. The correlation between age and size of field computed by the product-moment formula of Pearson for linear relationship is -0.31 ± 0.04. There is, however, a slight non-linearity of relationship shown in the table due to a pronounced shift towards smaller fields near 40 years of age. That is, above 40 years the mode occurs in the group 66–69.9 degrees (average 68), while below 40 years the mode occurs in the group 62–65.9 degrees (average 64). Be-

TABLE III

Showing the percentage of cases in each group of size of form field for each age group

AGE	AVERAGE BREADTH OF FORM FIELD (DEG.)					
	58–61.9	62–65.9	66–69.9	70–73.9	74–77.9	Total
years						
0–9			0.5			0.5
10–19		7.0	14.0	2.5		23.5
20–29	2.0	9.5	18.0	6.0	0.5	36.0
30–39	1.0	5.0	8.5	2.0		16.5
40–49	2.0	8.0	5.0			15.0
50–59		7.0	1.5			8.5
Total.....	5.0	36.5	47.5	10.5	0.5	100.0

tween 30 and 40 years a transitional stage is seen where there is more nearly an equal number of cases in the groups whose averages are respectively 68 and 64. This shift of the mode downward at age 40 and the transitional stage between 30 and 40 will be shown in a later paper to occur also for the color fields. The average size of field for the age group 10–19 is 67.0 degrees; for the age group 20–29 is 67.5 degrees; for the age group 30–39 is 66.8 degrees; for the age group 40–49 is 64.8 degrees and for the age group 50–59, 64.7 degrees.

In Figure 5 the data have been plotted to show separately the distribution of cases below and above 40 years of age. Curve A gives the distribution of the 153 cases below 40 years of age; Curve B the distribution of the 47 cases above 40 years of age. For ease of com-

parison the data for Curve B have been replotted in Curve C on a magnified scale. The factor of magnification used was 3.25, the ratio of the number of cases in the two groups.

It may further be noted that no very large fields (more than 70 degrees) occur above the age of 40 and no very small fields (less than 62 degrees) below the age of 20. These characteristics also are in general found for the color as well as the form fields.

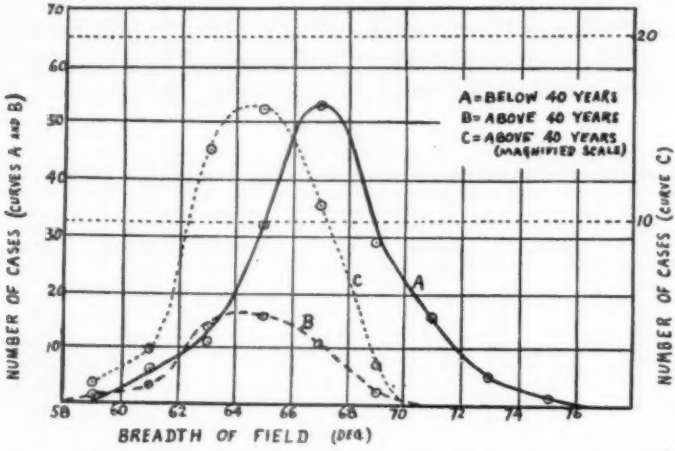

FIG. 5. SHOWING FOR COMPARISON THE DISTRIBUTION OF THE NONPATHOLOGICAL CASES BELOW AND ABOVE 40 YEARS OF AGE

In Curve A are represented the 153 cases below 40 years of age; in Curve B the 47 cases above 40 years of age; and in Curve C the cases above 40 years plotted on a magnified scale, the factor of magnification being 3.25, the ratio of the number of cases in the two age groups.

The narrower fields of the presbyopic group are probably largely a phenomenon of age rather than an effect of presbyopia. That is, presbyopia, loss of sensitivity and the general failure of all the powers of the eye are in the main coordinate rather than interdependent phenomena of age. However, in the more advanced cases of presbyopia the defective focussing for near seeing due to loss of accommodation doubtless exerts a direct influence on the results of perimetry when the stimulus is viewed at a distance of 33 cm. Other age phe-

nomena, extraneous to the functional changes in the sensory mechanism, which may exert an influence on the perimetric results, are opacities of the cornea, lens and vitreous, changes in pupil size, etc.

The results have further been studied to show what relation, if any, exists between sex and the size of the form field. The 200 cases studied included 84 males and 116 females. The median value of size of field rated in terms of average breadth is 66.4 degrees. For the males the

TABLE IV

Showing the number of cases of each sex studied in each refraction group and the average value of average breadth of field

REFRACTION GROUP	SEX	NUMBER OF CASES	AVERAGE VALUE OF AVERAGE BREADTH OF FIELD (DEG.)
Emmetropes	M.	22	67.42
	F.	28	67.73
Hyperopes	M.	28	66.42
	F.	47	67.54
Myopes	M.	12	64.98
	F.	18	65.25
Presbyopes	M.	17	64.54
	F	23	65.09
Mixed astigmatisms	M.	5	65.50
	F.	0	
Entire group	M.	84	66.04
	F.	116	66.75

average breadth of field for 36 cases or 43 per cent of the number tested falls above and for 48 cases or 57 per cent of the number tested below this value; for the females, the average breadth of field for 64 cases or 55 per cent of the number tested falls above and for 52 cases or 45 per cent of the number tested below this value. The average breadth of field for the males is 66.04 degrees; for the females 66.75 degrees.

Table IV gives the number of cases of each sex tested in the various refraction groups and the average breadth of field in degrees for each. It is seen that the averages for the females are slightly but consistently larger than for the males in each group. The differences are too small

to be significant for diagnosis but they present a possible point for further study. Whether they represent an actual difference in spread of sensitivity is problematic. The result may be due to other causes. Among these may be mentioned difference in facial conformation: the deeper set eyes, the more prominent nose, overhanging brows, etc., of the males. Some information as to the importance of the factor could be obtained perhaps from a study of the fields for the two sexes meridian by meridian. Sex differences and their analyses will be made the subject of more extensive study should the data obtained in later work show that the point is of sufficient importance.[8]

SUMMARY AND CONCLUSIONS

In former studies by two of the present writers, the factors which cause variability in the form and color fields for a given eye were determined and methods and apparatus were devised for their control. This has rendered the use of perimetry for the detection of the advance or recession of a pathological condition comparatively simple and easy. The use of perimetry in diagnosis, the other important application to clinic work, could be made equally easy if the same degree of control could be exercised over the factors which cause the results to vary from eye to eye. This degree of control has not yet been secured and in all probability can never be secured. At present the outstanding problem in clinical perimetry, therefore, is diagnosis.

The first step in diagnosis is the differentiation of the pathological from the nonpathological eye. In case of the form field this differentiation is based on two phenomena: changes in the size or extent of field and changes in the shape of field. Size of field, it is obvious, is more affected by the nonpathological factors which vary from eye to eye than is shape of field. The effect of these factors on size of field is to increase the range of variation for nonpathological eyes and the tendency to overlap the range for pathological eyes. For example,

[8] In this connection the following quotation taken from a letter written to one of the writers by Dr. Henry H. Donaldson of the Wistar Institute of Anatomy and Biology under date of March 26, 1926, is suggestive: "In studying the albino rat we have found the eye bulbs of the female to be heavier than those of the male of like body weight, and the area of the cross section of the optic nerve to be also greater in the female. This last would possibly suggest a slightly greater extension of the retina in the female."

the amount of contraction of field produced by a defect of refraction in a nonpathological eye may be as great or even greater than that produced by an incipient pathological condition in an emmetropic eye. In the use of perimetry for diagnosis it becomes necessary, therefore, to make for nonpathological eyes a careful determination of the range of variation of field for all of the outstanding, uncontrolled variables and for as many of them separately as is possible in our present state of knowledge. The knowledge of what is an *average* field, for example, can contribute but little to the diagnosis of borderline cases for which the help of perimetry is most needed.

It has been the purpose of the present study to determine the range of variation of the form field for nonpathological eyes for a stimulus subtending a visual angle of 1 degree. The cases studied were sampled to include as many as possible of the outstanding variables which are not pathological. Errors in refraction are found to be an important factor influencing the variability of result from individual to individual. After 40 years, age is also an important factor. Earlier than this the effect of age is negligible. Sex apparently is not a factor of sufficient importance to be taken into account in diagnosis. A scale has been formed showing the range of variation of field under the influence of these variables and the distribution or frequency of occurrence of the different sizes of field in a typical nonpathological group. Such a scale provides a means of placing each new case in the class or group to which it belongs, rated with regard to the distribution of normal cases, *i.e.*, it constitutes a scale for use in the separation of pathological from nonpathological cases.

In the formation of this scale it has been necessary that a single value or index be chosen to represent extent of field. Several values have been tried. Of these, average breadth of field in degrees and area of field in sq. cm. obtained from maps drawn to standard scale and measured with a planimeter were finally selected as the most feasible and satisfactory for diagnostic purposes.

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THE BACTERIAL FLORA AND HYDROGEN-ION CONCENTRATION OF THE LOWER HUMAN ILEUM; THE EFFECT OF LACTOSE AND ACIDOPHILUS MILK ADMINISTRATION; AND THE POSSIBLE RELATIONSHIP OF ILEAL FLORA TO CHRONIC ULCERATIVE COLITIS[1]

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Our knowledge of the human ileum by no means is comparable with our not too complete information of the human colon. Obviously, the inability of access in living subjects is responsible for this disparity.

It has been the purpose of this study to ascertain simultaneously the flora and the reaction of the lower human ileum in living subjects upon whom complete transverse ileostomies had been performed and in whom the ileums could be regarded as normal. Observations over relatively long periods of time and under varying conditions have been made so as to note deviations *within* as well as between individuals, a type of information obviously impossible to secure from autopsy material. The possibilities in regard to the transforming effect of lactose and acidophilus milk upon ileal flora and the effect of these products upon the ileal reaction also have been noted, and finally an attempt has been made to correlate the ileal flora, as a result of the findings here, with the flora noted in some cases of ulcerative colitis.

MATERIALS AND METHODS

Three persons upon whom complete transverse ileostomies had been performed 25 to 30 cm. (10 to 12 inches) above the ileo-cecal valve, for the relief of idiopathic ulcerative colitis, were studied. In each case, the ileum above the point of severance was regarded as normal for reasons to be found under "Discussion." In each case

[1] Presented before the American Gastro-Enterological Association, at Washington, D. C., May 1, 1928

the free and total acids fell within normal limits. Case 1 was a male, 27; case 2, a married woman, 28; and case 3, a youth of 16. During the course of this study all were partaking of a highly nutritious and well balanced diet after the fourth post-operative day. The procedures in this investigation were as follows:

In each instance in which material was secured, the lips of the protruding ileum were wiped with sterile gauze. They were then separated with a sterile clamp so that each of the several sterile swabs (1) inserted on each occasion from 3 to 5 inches beyond the opening would not touch the surface either upon entry or withdrawal from the intestine. Two material-containing swabs were then washed immediately in 2 to 3 cc. doubly distilled water and the hydrogen-ion concentration of the ileal content or scrapings was determined within five to ten minutes thereafter by the use of 2 to 5 drops of this emulsion. Here the colorimetric micro method of Brown (2) was employed. Another swab was used for the making of a gram-stained smear to ascertain, in a general way, the type of flora present. Still another was used in the making of direct aerobic and anaerobic blood agar plates for the purpose of isolating organisms and ascertaining the relative numbers of the various forms present.

Excepting in case 3, studied for two days previous to closure of an ileostomy of six months during which time the large bowel had completely healed, (as determined by the method of Stone (3) as well as by sigmoidoscopic and roentgenologic examinations) and in cases 1 and 2 from material secured immediately after the opening of each ileostomy as well as from material secured in case 2 on the fifth post-operative day, no direct smear and no direct blood agar plates were made, for the study had not then assumed its definite direction and purpose. In these instances the hydrogen-ion concentration was determined as already noted, and one loopful of a bouillon dilution, made by washing the swab containing ileal content or scrapings in 5 cc. infusion bouillon, was placed in each of the following media which were then grown aerobically and anaerobically for 24 and 48 hours, respectively: cooked meat, cooked meat with dextrose, pancreatic digest broth, infusion broth, dextrose broth, serum broth and dextrose serum broth. It will be noted that, although in these same instances the hydrogen-ion determinations appear on the graphs,

because of the differences in bacteriologic procedures in these instances, the results will be recorded only under "Observations."

Gram-stained smears were studied as follows: at least four widely scattered fields were observed and the average percentages of the various types of organisms present were noted. In regard to the blood agar plate method, the media employed and the procedure followed were essentially those described by Brown (4) in his monograph on streptococci. The aerobic plates were incubated for 24 hours and refrigerated for a like period. The anaerobic plates were so made by placing blood agar plates in Brown's anaerobic jar (5). This jar was then incubated for 48 hours and refrigerated for a like period, after which the number of each variety of colony was ascertained on both aerobic and anaerobic plates and the organisms were determined in a general way.

Frequently the morphologic characteristics between diphtheroids, diplo-bacilli, Gram-positive bacilli and diplococci were not clear upon Gram-stained smears made from colonies on blood agar plates. In these instances the questionable colonies were placed in liquid media for from 24 to 48 hours when final determinations were made from Gram-stained smears of the latter. Those colonies showing Gram-negative bacilli were introduced into each of three Durham tubes containing, in 5 cc. of extract bouillon, the test substances of either lactose, dextrose, or saccharose; brom-cresol purple was the indicator used. Gram-positive bacilli isolated on anaerobic plates were placed in a medium of milk and 0.2 per cent peptone under a petrolatum cap to determine gas formation (*B. welchii*).

The effect of lactose and acidophilus milk upon the ileal hydrogen-ion concentration and flora was also studied in case 1. This patient was fed subsequently to the foregoing research, in addition to his well balanced diet, 1000 cc. acidophilus milk and 100 grams lactose daily, for eight consecutive days. This study was begun on the third day of this dietary and continued daily until the end of the eighth day. Material was taken from his ileum, the hydrogen-ion concentration determined and Gram-stained smears made in exactly the same manner as already described. The blood agar plate studies as to number and variety of colonies were also the same as heretofore noted, except that dextrose acid agar was used instead of infusion agar in the making

of blood plates and that these plates were incubated for 24 hours and refrigerated for a like period under partially anaerobic conditions. Partial anaerobiosis as well as dextrose acid agar were employed to encourage the growth of *L. acidophilus*. Partial anaerobiosis was brought about by creating a partial vacuum of 55 cm. Hg. in a Brown anaerobic jar containing the blood plates, by means of a vacuum pump.

OBSERVATIONS

As will be observed in chart 1, case 1 was studied over a period of 45 days following ileostomy. The hydrogen-ion concentrations fluctuated between pH 8.3 on the sixth day to 7.3 on the fortieth day. At no time was the ileum acid in reaction regardless of type of food ingested or the time of the day during which the material was secured. The average pH determination was 7.65. Chart 1 shows the relative percentages of organisms found on direct ileal smears: Gram-positive bacilli preponderated only on the 37th day; on the 40th and 44th days there were about as many cocci in evidence as Gram-positive bacilli; on all other occasions cocci predominated. It is interesting to note that in no instance did Gram-negative bacilli dominate the field.

The plates (see Chart 1) did not, as a rule, show the same relationship in regard to the proportion of the various types of organisms present as that noted on direct smears. On the thirty-third, thirty-fifth, thirty-eighth, forty-first, forty-second and forty-fifth days cocci predominated on Gram-stained smears. In the first instance (thirty-third day) the plates showed only cocci aerobically and Gram-positive bacilli and cocci anaerobically; in the second instance (thirty-fifth day) there was a complete absence of Gram-positive bacilli on all plates although the original smear showed their presence to be about 10 per cent of all organisms present. Four-fifths of all organisms noted on the ileal smear of thirty-eighth day were cocci, yet no such huge preponderance appeared on plates. A similar situation prevailed on the forty-second day. The smear on the forty-fifth day revealed a dominance of cocci but the organisms were few in number and no plate growth was secured. On the fortieth and forty-fourth days, the material secured revealed an equal number of cocci and Gram-positive bacilli on smears, yet a majority of cocci were noted on plates.

In only six instances did Gram-positive bacilli cause gas formation in milk under a petrolatum cap—*B. welchii*. In most instances in

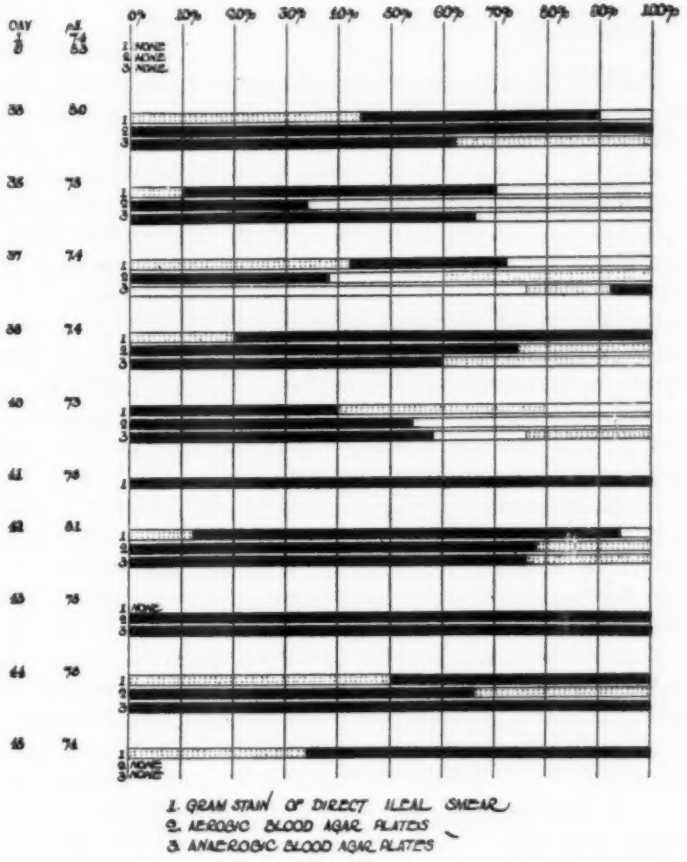

CHART 1. CASE 1. THE BACTERIAL FLORA AND HYDROGEN ION CONCENTRATION OF THE LOWER HUMAN ILEUM ON A FULL, WELL BALANCED DIET

For key, see chart 3

which Gram-negative bacilli were found on plates, upon cultivation in lactose and dextrose, acid and gas were formed; some so affected

saccharose, others did not—*B. coli* group. In a few instances, Gram-negative organisms did not ferment dextrose, saccharose or lactose, and in each case were motile (*B. alkaligenes*). No further studies were made with Gram-negative bacilli.

Case 2 was observed over a period of 48 days (see Chart 2). The hydrogen-ion concentration determined at 20 irregular intervals during this period, irrespective of the type of food ingested or the time of day during which the material was secured, was alkaline, save in one instance, on the forty-fifth day, when it was slightly acid—pH 6.8. The average for pH determinations was 7.47. The flora was studied on eighteen occasions during the same period. Save on the ninth day when direct ileal Gram-stained smears showed no organisms, and that of the thirty-sixth day which revealed a preponderance of cocci, all Gram-stained ileal smears showed a preponderance of Gram-positive bacilli. Cocci, however, were next numerous and Gram-negative bacilli least in relative numbers. Here too the plates more often failed to show a similar relationship of types of organisms as noted on corresponding smears. For instance, on the thirty-sixth day when the smear showed a great number of cocci (see Chart 2) the aerobic plates revealed only Gram-negative bacilli, while the anaerobic plates showed chiefly Gram-positive cocci. The aerobic plates revealed the same picture on the third, fifteenth and sixteenth days while the smears revealed a preponderance of Gram-positive bacilli also on the twenty-sixth, thirtieth, thirty-eighth and forty-first days, yet cocci predominated on both aerobic and anaerobic plates. The aerobic plates of the thirty-seventh, forty-fifth, forty-eighth days showed no growth; however, Gram-positive bacilli predominated on the anaerobic plate of the thirty-seventh day and cocci on the anaerobic plates of the forty-fifth and forty-eighth days. Gram-negative bacilli predominated on both aerobic and anaerobic plates of the twenty-eighth and thirty-fourth days, cocci predominated on the aerobic plate and Gram-positive bacilli on the anaerobic plates of the forty-third day, Gram-positive bacilli predominated on the anaerobic plates and no growth appeared on the aerobic plates of the thirty-third day, and no growth appeared on either type of plate on the fourteenth and seventeenth day; yet direct smears on these occasions revealed a preponderance of Gram-positive bacilli, save on the twenty-eighth

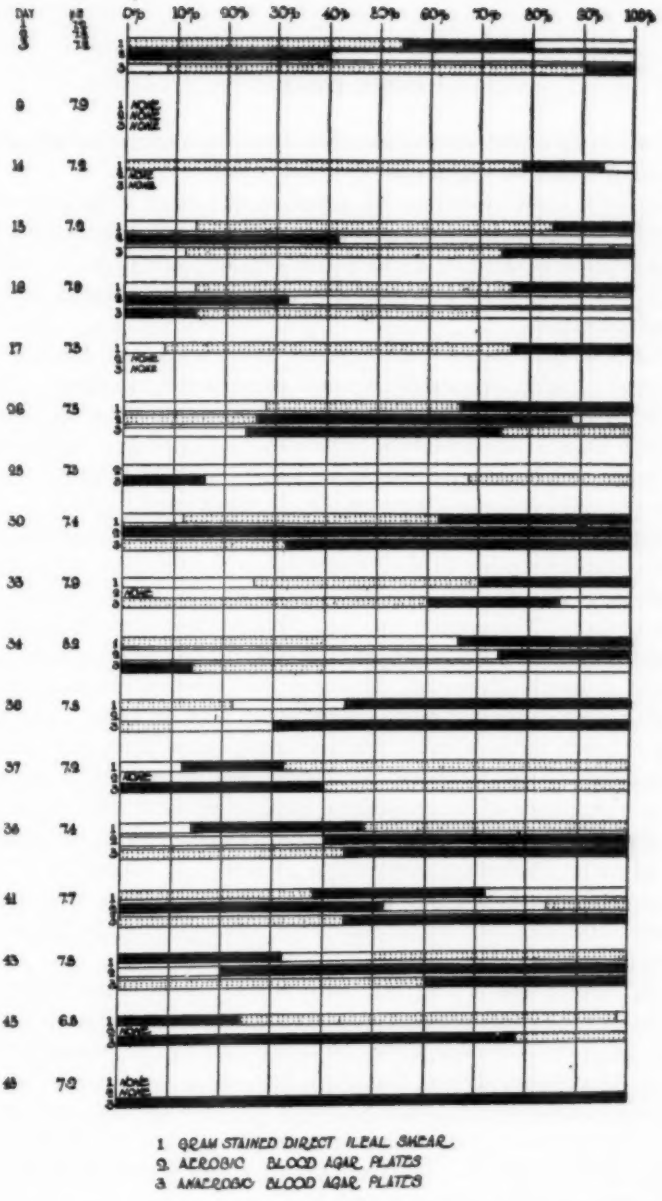

CHART 2. CASE 2. THE BACTERIAL FLORA AND HYDROGEN ION CONCENTRATION OF THE LOWER HUMAN ILEUM ON A FULL, WELL BALANCED DIET

For key, see chart 3

day when no smear was made and on the forty-eighth day when the smear revealed no organisms.

On only eight occasions did a few of the many isolated Gram-positive bacilli from anaerobic plates produce gas in milk and 0.2 per cent peptone covered by a petrolatum cap, indicating that *B. welchii* were few in number and that they could not be frequently and readily isolated.

The experience with Gram-negative bacilli from both aerobic and anaerobic plates was similar to that encountered in case 1. They were isolated whenever colonies were discovered on either plate. Nearly always they fermented lactose and produced gas. In isolated instances Gram-negative organisms failed to ferment dextrose, saccharose and lactose and were motile (*B. alkaligenes*).

The third case, a youth of 16, was observed once on each of two successive days prior to the closure of an ileostomy of six months' duration. The reaction was pH 7.6 on one day and 7.2 on the following day. The average was 7.4. When this case was studied the exact nature of this research was not clear and no direct smears were made, as previously noted. However, ileal scrapings on each of two days placed in cooked meat, cooked meat with dextrose, pancreatic digest broth, infusion broth, dextrose broth, serum broth and dextrose serum broth, and incubated aerobically and anaerobically, revealed a predominance of Gram-positive cocci: diplococci, enterococci, or streptococci, regardless of the method of incubation or type of medium employed. Diplococci grew more profusely in serum broth and in cooked meat and not so well in infusion broth. There were more Gram-negative bacilli and fewer Gram-positive bacilli in the aerobic media.

In cases 1 and 2 ileal scrapings secured immediately after the opening of the ileostomies, were placed in the media and grown under the same conditions as above mentioned in case 3. Gram-positive cocci predominated here, also, regardless of the type of medium and of the method of incubation although the growths were very scant. The hydrogen-ion concentrations were pH 7.4 and 7.2, respectively (see Charts 1 and 2). No direct smears or plates were made here for the same reason as given for case 3.

THE EFFECT OF LACTOSE AND ACIDOPHILUS MILK UPON THE FLORA AND pH OF THE HUMAN ILEUM

Case 1, subsequently to the foregoing research, was fed daily for a period of eight consecutive days, in addition to his well balanced diet, 1000 cc. of acidophilus milk and 100 grams of lactose. The bacteriological study was begun on the third day of this dietary, because Cheplin and Rettger (6) have shown that the human fecal flora can be transformed under this regimen as early as the third day. The procedures have already been described under "Materials and Methods of Study."

Hydrogen-ion determinations were made on eight occasions; in seven instances the material secured for such determination was secured directly from the ileum. On one occasion (eighth day) for comparative study material was secured simultaneously from the ileum and from a cup worn by the patient which contained ileal content. Both specimens showed a pH of 7.3. The average reading for eight hydrogen-ion concentrations, one or more determinations having been made daily over the last five days of an eight-day observation, was pH 7.46. This is to be compared with the average reading of 7.65 secured in this case on a well balanced dietary minus lactose and acidophilus milk. The Gram-stained ileal smears showed a paucity of organisms here as compared with smears in the other phase of this study. In all instances, cocci predominated.

In three instances, on the sixth, seventh and eighth days, smears were made from the ileal content in the cup worn by the patient for comparison with material secured directly from the ileum. Cocci predominated in all instances in gram-stained smears (see Chart 3).

The flora was transformed in that cocci averaged more than sixty per cent of the organisms to be seen on smears; *L. acidophilus* averaged somewhat more than 19 per cent, Gram-positive bacilli somewhat more than 9 per cent, and Gram-negative bacilli slightly more than 7 per cent. The numbers of cocci were increased, the numbers of Gram-positive (other than *L. acidophilus*) as well as Gram-negative bacilli were reduced as compared with the flora in this case prior to the ingestion of acidophilus milk and lactose. The dextrose blood agar plates incubated under partial anaerobiosis did not show a predominance of characteristic *L. acidophilus* colonies. As a matter of fact here the

plates virtually coincided with the smears—cocci predominating on all plates except those of the eighth day, when an equal number of Gram-negative bacilli and Gram-positive cocci colonies were present.

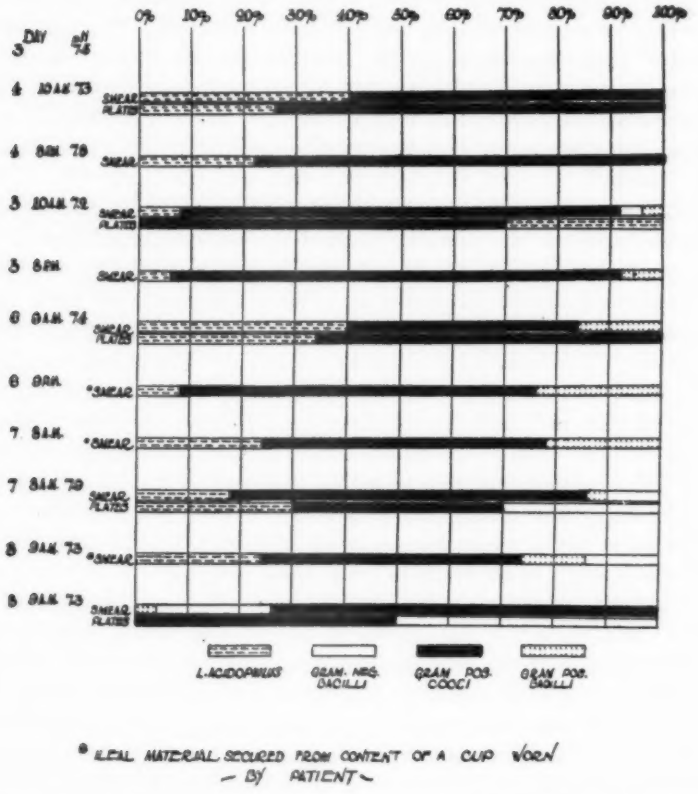
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
L. ACIDOPHILUS
GRAM. NEG. BACILLI
GRAM POS. COCCI
GRAM POS. BACILLI
* ILEAL MATERIAL SECURED FROM CONTENT OF A CUP WORN — BY PATIENT —

Chart 3. Case 1. The Effect of the Addition of Acidophilus Milk and Lactose to a Well Balanced Dietary on the Bacterial Flora and Hydrogen Ion Concentration of the Lower Human Ileum

The character of the ileal discharge which at first was liquid, somewhat bright yellow in color but which later became brown, fairly well

formed yet non-fecal in odor, changed on the third day of this phase of the study to a bright yellow liquid, also non-fecal in odor, which proved to be very corrosive in its action upon the abdomen of the patient.

DISCUSSION

The human ileums under investigation have been regarded as free from organic disease. In each case, the ileostomy was performed from 25 to 30 cm. (10 to 12 inches) above the ileo-cecal valve. At this point the surgeon was relatively certain that he had allowed a safe margin above the ileo-cecal valve at which place, in these cases, the disease appeared to have terminated. As a matter of fact, at the operation each ileum appeared normal, and at no time during the course of this research did that part of the mucous membrane of the proximal portion of the ileum attached to the abdominal wall, visible to the eye, ever appear involved. Besides, such a condition as possible alteration in the function of each ileum, as noted by some change in color and consistency of the excreta occurring in a short while after the institution of the ileostomies, resulted in no definite variation in either the bacteriological results or in the hydrogen-ion determinations in any case. Hence we have looked upon these ileums as normal.

The terminal human ileum, as a result of this study, appears to be alkaline in reaction. In these three cases where hydrogen-ion concentrations were determined in 42 instances under various conditions and dietaries, the pH was slightly acid on one occasion only. These findings seem contrary to the notion of terminal ileal acidity established as early as 1894 by Macfayden, Nencki and Sieber (7), and also by Ciechomski and Jakowski (8) in the same year, from fistulae by the litmus paper test, and by subsequent investigation upon animals by others. However, our results are in line with the work of Van der Ries (9) who found that the pH is higher (more alkaline) in the upper human jejunum than in the duodenum, higher in the lower jejunum than in the upper, and assumes that it is still higher in the ileum, in other words, that acidity in the intestine decreases on the way down. This is emphasized by the work of McClendon, Myers, Culligan and Gydeson (10) on laboratory animals. They demonstrated that the longer the ileum the greater is the absorption of carbon dioxide liber-

ated by the gastric juice, and the greater this absorption, the greater is the tendency toward alkalinity. Brown (11) in a single determination of the reaction of dejecta from an ileostomy, found it to be pH 7.4 by the colorimetric method of Clarke.

It is believed in some quarters that diet seems to bear no relationship to reaction. McClendon, Shedlov and Thompson (12) showed that the ileal content of puppies, whether fed on milk or on solid food, had a similar reaction varying from pH 5.7 to 6.34. McClendon, Shedlov and Karpman (13) showed further that the reaction of the ileal content of dogs when fed on a mixed diet of cooked food varied from pH 6.3 for the first part, 5.6 for the middle portion, and 6.6 for the terminal portion. In this same connection it might be interesting to note that Cheplin and Rettger (14) state that a diet enabling one to change fecal flora is not sufficient to alter the hydrogen-ion concentration of the feces. However, in regard to the terminal human ileum, we found in case 1 (see Chart 3) that during the administration of lactose and acidophilus milk to a well balanced dietary its hydrogen-ion concentration was alkaline, pH 7.46—and within the range of the average of the pH determinations secured when the patient partook only of a well balanced dietary without the lactose and acidophilus milk, pH 7.65, yet a comparison of the former pH average with the latter may indicate that lactose and acidophilus milk played some rôle in the lowering of the hydrogen-ion concentration. It is suggested that deviations in the reaction with changes in diet in other portions of the intestinal tract might have been noted, had *averages* of comparative determinations in the same individual been considered rather than single determinations.

It will be noted that in the three cases studied the ileal flora was dominated, in each instance, by Gram-positive organisms. In each of the two cases where nothing had been ingested for about eighteen hours (a period of more than twelve hours prior to the ileostomy and of some hours subsequent to the operation until the opening of the complete ileostomy by cautery was accomplished) organisms were to be found in the ileum. They were few in number and consisted chiefly of Gram-positive cocci, and bacilli. This is contrary to Cushing's (15) viewpoint in regard to the human jejunum. He held that the flora was dependent on the type of food ingested, that the jejunum in the absence of the ingestion of food was free from organ-

isms, and that, therefore, the jejunal flora was not stable. Our findings in the lower human ileums indicated that the presence of organisms was to be encountered regardless of the phase of ingestion or digestion, and that we were in accord with those of Ganter and Van der Ries (16) who found a constant flora in the empty post-absorptive small intestine. Bogendörfer (17) securing human intestinal content through tubes previously swallowed and estimated as being from 100 to 200 cm. from the pylorus, concluded that the bacteriological picture over this wide area was uniform He noted many diplococci, enterococci, and staphylococci as well as Gram-positive and Gram-negative bacilli. He believed the flora to be obligate to which *B. coli* did not belong. Van der Ries virtually reached the same conclusions.

It will be further noted that there was no close relationship between the relative number of various types of organisms noted on plates as compared with smears. This merely indicated that the direct smear gave the best estimate of the relative proportions of the various types of bacteria present, and that those organisms which appeared in greater number in media were those which thrived best in the type of cultivation employed.

In case 1, following the previously described research on ileal flora when free from ingesta and when on a well balanced diet, the daily addition of a quart of acidophilus milk and 100 grams of lactose to the usual well balanced diet for a period of eight days showed a change in the ileal excreta at the beginning of the fourth day. Previously it had changed from a thin, yellowish discharge to that of one fecal-like in color but not in odor, and mushy in consistency. Now, under the influence of the addition of lactose and acidophilus milk to the daily dietary regimen, the discharge became watery, yellowish and corrosive in its action on the skin, but remained non-fecal in odor. This watery change persisted during the remainder of this phase of study. This alteration in the character of the excreta in the human ileum is interesting because of the relief from constipation afforded many patients upon the administration of acidophilus milk. Besides, regardless of the phase of ingestion of the acidophilus milk and lactose, the total number of organisms noted on the direct smears was much less than those seen on direct smears when the patient had not partaken of lactose and acidophilus milk. No explanation is offered for this apparent diminution of organisms.

The most striking finding seemed to be this: that while Cheplin and Rettger (18) have demonstrated that by the end of the third day on the aforementioned dietary, the fecal flora can be altered so as to evidence a preponderance of *L. acidophilus*, at no time did it appear that *L. acidophilus* predominated in the human ileum either on smear or on dextrose blood agar plates. The ileal flora seemed to be altered by showing a marked preponderance of cocci at the expense of Gram-negative and Gram-positive bacilli. So it would seem that this flora may be affected by acidophilus milk and lactose; that *L. acidophilus* either is washed down or may multiply to some extent in the small intestine, and that it is in the large intestine where, according to the work of Cheplin and Rettger, it more markedly transforms and simplifies the flora. Here there seemed to be a close relationship between the relative number of various types of organisms noted on smears and on corresponding plates. As already noted and discussed, the reaction of the ileum was made somewhat less alkaline by acidophilus milk and lactose.

THE POSSIBLE RELATIONSHIP OF ILEAL FLORA TO COLITIS

For years it has been believed, here and there, that certain pathologic conditions in man are associated with the intestinal flora. Various disorders, digestive and otherwise, have been attributed to the effect of, first, one type of bacterial flora and then that of another. Any deviations in the supposedly normal flora, or the preponderance of one type of organism usually not predominant over that of another, has been associated, from time to time, with various and sundry conditions. Some observers have claimed that, because a Gram-positive flora is often seen in cases of idiopathic ulcerative colitis, such a finding is significant as to etiology. As a matter of fact, in our own work on ulcerative colitis (19), such a flora too was occasionally seen. However, as a result of this research, the suspicion arose that this type flora could be accounted for by the Gram-positive flora of the ileum, with its many cocci, being brought down to the involved rectum and sigmoid by the hypermotility of the large bowel. In the rectum and sigmoid, in the presence of blood, mucus and pus, these cocci then multiplied and dominated the scene. That such a situation might readily be the case, was strengthened by the work of Garrod (20) of St. Bartholomew's Hospital, London, who demonstrated that

24 hours after the administration to a normal individual of the first of a series of daily aperients, daily smears made from fresh fecal specimens revealed streptococci numbering between 90 and 100 per cent of all organisms present. This worker further observed in another normal individual that when constipation was induced by morphia, streptococci were reduced from 80 to 10 per cent; in the same individual subsequent saline aperients increased the numbers to almost 100 per cent within two days. Garrod felt that the source of these streptococci had been ascertained when he removed the intestine of a human subject dead 24 hours, studied the bacterial flora at varying levels and found that the greatest number of streptococci were in the last three feet of the human ileum. This study which appeared defective in that the source of material had been dead for 24 hours (from a fractured skull) assumes its proper significance in the light of our studies.

SUMMARY

Three cases upon whom complete transverse ileostomies had been instituted for the relief of idiopathic ulcerative colitis were studied as to flora and reaction of the lower ileum, the effect of the administration of lactose and acidophilus milk, and the possible relation of ileal flora to chronic ulcerative colitis. These ileums were regarded as normal.

1. In 43 determinations, regardless of the type or amount of food ingested or of the phase of digestion, it was found that the hydrogen-ion concentration of the lower human ileum was alkaline, save in one instance when it was slightly acid.

2. It was found that the ileal flora, under similarly varying circumstances always showed a preponderance of Gram-positive organisms. In two cases cocci predominated; in the other case Gram-positive bacilli (not *B. welchii*) were in the majority, cocci being next in number. In the ingesta-free ileums a few organisms were to be found: chiefly cocci and some Gram-positive bacilli.

3. It was found that *L. acidophilus* and lactose, added to the well-balanced diet of one patient, and administered in sufficient quantities, according to Cheplin and Rettger, to alter the fecal flora with a predominance of *L. acidophilus*, resulted not in an actual preponderance of the latter, but in an increase of cocci at the expense of Gram-

positive and Gram-negative bacilli, thus indicating that there may be some alteration of the ileal flora under such circumstances, and that *L. acidophilus* either is washed down or may multiply to some extent in the human ileum. The degree of ileal alkalinity was somewhat reduced by the above-mentioned addition to the daily dietary.

4. It was found that the normal ileal flora may bear a relation to the Gram-positive flora noted in some cases of chronic ulcerative colitis. In the latter instances the hypermotility of the large intestine could account for the presence of the ileal flora in the affected parts of the colon where blood, mucus and pus might result in a multiplication of the large numbers of cocci brought down from the ileum.

I am indebted to my chief, Dr. Thomas R. Brown to Dr. J. Howard Brown for his suggestions and advice, and to Dr. Harvey B. Stone for his co-operation in furnishing material.

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BOOK REVIEWS

Thrombo-angiitis Obliterans. Clinical, Physiologic and Pathologic Studies. By George E. Brown and Edgar V. Allen, Division of Medicine, Mayo Clinic. Collaborating in Pathology with Howard R. Mahorner, Fellow in Surgery, The Mayo Foundation, Rochester, Minn.

A careful, painstaking review of a condition that is most unsatisfactory to the doctor, while being disastrous to the patient. Nothing new, nothing startling. As others have done, so these authorities have exhausted every avenue of investigation in the attempt to discover some clue as to the cause of thrombo-angiitis obliterans, with negative results. Like everyone else, too, they feel that the use of tobacco is of some importance but that too great stress must not be laid upon it. It is interesting to note that considerable improvement has followed the treatment with non-specific protein, as exemplified in the use of triple typhoid vaccine. We have not had the same experience in Baltimore.

As regards the site of amputation, it is our feeling that too great stress is laid on amputation below the knee at the Mayo Clinic. It is true that a considerable portion of patients can stand this, but too often the stump is not what it should be, and since thrombo-angiitis obliterans is a progressive condition, ulceration accompanied by pain tends to recur with the result that amputation above the knee not infrequently has to be done. It is our feeling that if an amputation has to be done at all, most patients are much better off with a removal just above the knee.

The lumbar ganglionectomy as carried out by Adson of the Mayo Clinic is mentioned and rather stressed, but the authors feel that any beneficial results that might come from it would depend much upon the proper selection of cases. They further say that in their experience only about one in every seven cases met the requirements. The same thing might be said with regard to their other forms of treatment advised for relief of the condition. It is the reviewer's feeling that lumbar ganglionectomy is a rather radical procedure to adopt in a condition of this kind and until many more successful cases have been done by competent operators, it had best not be adopted by the rank and file of surgeons. It hardly seems as if it will stand up in future years as a real method of dealing with thrombo-angiitis obliterans. LeRiche's periarterial sympathectomy is much less of an ordeal and, if carefully done, seems to offer more relief.

For those interested in vascular conditions in general, physicians as well as surgeons, a copy of this study is well worth having.

B. M. B.

A Text-Book of Psychiatry. For Students and Practitioners. By D. K. Henderson, M.D. (Edin.), F.R.F.P.S. (Glas.) and R. D. Gillespie, M.D. (Glas.), D.P.M. (Lond.) 520 pp. $5.50. (*Oxford University Press, New York, 1927.*)

Practical Clinical Psychiatry. For Students and Practitioners. By Edward A. Strecker, A.M., M.D., and Franklin G. Ebaugh, A.B., M.D. Second edition, enlarged and revised. 458 pp. $4.00. (*P. Blakiston's Son and Company, Philadelphia, 1928.*)

These two books, both of which should be widely read, are of special interest because Henderson and Gillespie, as well as Ebaugh, are pupils of the Rhipps school. The aim of both books is therefore "to present psychiatry as a living subject, with important relations not only to general medicine, but to the social problems of everyday life."

Henderson and Gillespie start with a historical review and then discuss the various systems of classification. They use Adolf Meyer's "types of reaction" as the general scheme. The many well presented case histories illustrating the various reaction types not only give the student an understanding of the complexity of psychiatric patients but also point out the features they have in common with other cases of the same type of reaction. It is not a textbook with rare selected cases but one filled with life material. It might possibly be easier for the student, however, if some of the essential symptoms of the various reaction-types were more stressed. One great advantage presented by this book is the acceptance of the individual case treatment instead of the tendency to dispose of a whole group with a general outline. The great value of this is especially illustrated in dealing with the manic-depressive psychoses, where, instead of a fatalistic attitude, we find the following: "Perhaps the most important thing of all in the way of treatment is to give the patient some better understanding of the factors which have been responsible for the illness, so as to prevent a possibility of recurrence." The authors discuss the current opinions and give many references on the various topics, but this method may occasionally be distracting to a reader who would prefer to have the fundamentals presented from the authors' own viewpoint. A brief but full presentation of symptomatology and an outline of the method of examination are very helpful. General psychopathology is unfortunately written from a rather one-sided point of view and often not quite in harmony with the rest of the book. Many readers might also need more facts on the relation of psychoneuroses to other domains of medicine. In a second edition the American reader would appreciate a résumé of the fundamental and guiding legal ideas of this country as well as of Great Britain.

Strecker and Ebaugh's second edition shows some valuable additions, but the whole plan is unchanged. The case method of presentation is chosen, classical cases are somewhat neglected, but pictures of patients are used in whom the disease has occurred in actual life. The authors emphasize the treatment not only of physical symptoms but also of the patient's personality,—"in fact the entire

patient." Diagnostic points are well stressed and summarized, impressing upon the reader the most important symptoms and symptom-complexes. General psychopathology finds but little space; treatment is also rather brief, but due space is given now to the modern therapy of paresis. The book is especially suited for the beginner in psychiatry.

O. D.

Tumors Arising from the Blood-vessels of the Brain. Angiomatous Malformations and Hemangioblastomas. By HARVEY CUSHING and PERCIVAL BAILEY. 219 pp. $7.50. (*Charles C. Thomas, Springfield, 1928.*)

Realizing the relative rarity of tumors of the blood vessels within the cranial cavity, it is only natural that the readers of this new monograph by Cushing and Bailey should find that the greater part of the compilation consists of clinical observations rather than critical studies of pathological specimens. When the full significance of the statement of these authors is realized, namely, that the diagnosis of these tumors is difficult and often, in certain groups, quite accidental, and that any attempt at surgical or other treatment is unsatisfactory, one is not surprised to find that material satisfactory for detailed studies in the cases belonging to this group of tumors was rarely obtainable. As much, however, as was available seems to have been carefully studied and one feels that the record constitutes a contribution. Such clinico-pathological studies as this one by Cushing and Bailey always find a place of usefulness especially in the surgeon's library.

W. D. F.

A Handbook for the Diabetic. By ALBERT H. ROWE, B.S.M.S.M.D. 129 pp. (*Oxford University Press, New York, 1928.*)

To the list of small volumes designed as guides for the diabetic patient, we welcome this book. It is well bound, the type is clear, and the subject matter has been well arranged. Technical terminology has been carefully avoided, as is proper in a medical book designed for the layman. Of especial interest is the chapter on Etiology because of its complete, yet concise, review of the subject. The chapter on "The Present Outlook for the Diabetic" answers many of the common questions put to the doctor by the patient. It is conservative, yet hopeful.

Insulin, what it is and its use, Diabetic Arithmetic and Diet, Safeguards for Health and Food Values are other subjects discussed. In the "Tables of Food Values" the inclusion of Vitamin and Mineral content of the various foods may be of value to the physician but, one would fear, tends to be somewhat confusing to the patient who already has the worry of determining the proper, P, F and CH value of the diet. The blank pages at the end of the book should be very welcome to thoughtful patients.

E. J. L.

BOOKS RECEIVED

Oxford Medical Publications. Publisher: Humphrey Milford, London. The following nine volumes:

Diseases of the Larynx. Including Those of the Trachea, Large Bronchi and Oesophagus. By HAROLD BARWELL, M.D. (Lond.), F.R.C.S. (Eng.). Third Edition. 1928. 8°. 278 pages.

Diagnosis and Treatment of Deformities in Infancy and Early Childhood. By M. F. FORRESTER-BROWN, M.S., M.D. (Lond.). With a foreword by Sir Robert Jones, Bart., K.B.E., C.B., F.R.C.S. 1929. 8°. 199 pages.

The Cytoarchitectonics of the Human Cerebral Cortex. By CONSTANTIN VON ECONOMO. Translated by Dr. S. Parker. 1929. 8°. 186 pages.

Tweedy's Practical Obstetrics. Edited and largely re-written by Bethel Solomons, M.D., F.R.C.P.I., M.R.I.A. Sixth edition. 1929. 8°. 759 pages.

Oesophageal Obstruction. Its Pathology, Diagnosis and Treatment. By A. LAWRENCE ABEL, M.S. (Lond.), F.R.C.S. (Eng.). 1929. 8°. 234 pages.

Nephritis. Its Problems and Treatment. By T. IZOD BENNETT, M.D. (London), F.R.C.P. 1929. 8°. 94 pages.

Tuberculosis. Its Prevention and Home Treatment. A Guide for the Use of Patients. By HYSLOP THOMSON, M.D., D.P.H. Third edition. 1928. 12°. 99 pages.

Haemorrhoids. Their Aetiology, Prophylaxis and Treatment by Means of Injections. By ARTHUR S. MORLEY, F.R.C.S. Eng. Fourth impression, revised and enlarged. 1929. 8°. 122 pages.

The Robert Jones Birthday Volume. A Collection of Surgical Essays. 1928. 8°. 434 pages.